# In the United States Court of Federal Claims

**OFFICE OF SPECIAL MASTERS**

Filed: December 21, 2023

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| ROBERT JOSEPH GARDNER, | * | |
| Petitioner, | * | No. 17-1851V |
| v. | * | Special Master Gowen |
| SECRETARY OF HEALTH AND HUMAN SERVICES, | * | Entitlement; Off-Table Injury; Significant Aggravation; Influenza ("Flu") Vaccination; Multiple Sclerosis ("MS"). |
| Respondent. | * | |

*David Charles Richards,* Christensen & Jensen, P.C., Salt Lake City, UT, for petitioner.
*Kimberly Shubert Davey,* U.S. Department of Justice, Washington, D.C., for respondent.

## RULING ON ENTITLEMENT[1]

On November 29, 2017, Robert Joseph Gardner ("petitioner"), filed a petition for compensation under the National Vaccine Injury Compensation Program.[2] Petitioner alleged causation-in-fact between an influenza ("flu") vaccine which he received on December 1, 2014, which caused him to suffer acute disseminated encephalomyelitis ("ADEM") and/or that the flu vaccine caused or significantly aggravated his multiple sclerosis ("MS"). Petition at Preamble (ECF No. 1). After review of all of the evidence submitted by the parties,[3] for the following reasons, I find that Petitioner has presented preponderant evidence that the influenza vaccine

[1] Pursuant to the E-Government Act of 2002, *see* 44 U.S.C. § 3501 note (2012), because this decision contains a reasoned explanation for the action in this case, I am required to post it to a publicly available website. This decision will appear at https://www.govinfo.gov/app/collection/uscourts/national/cofc or on the Court of Federal Claims website. **This means the decision will be available to anyone with access to the Internet.** Before the decision is posted on the court's website, each party has 14 days to file a motion requesting redaction "of any information furnished by that party: (1) that is a trade secret or commercial or financial in substance and is privileged or confidential; or (2) that includes medical files or similar files, the disclosure of which would constitute a clearly unwarranted invasion of privacy." Vaccine Rule 18(b). "An objecting party must provide the court with a proposed redacted version of the decision." *Id.* **If neither party files a motion for redaction within 14 days, the decision will be posted on the court's website without any changes.** *Id.*

[2] The National Vaccine Injury Compensation Program is set forth in Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755, codified as amended, 42 U.S.C. §§ 300aa-10 to 34 (2018) (hereinafter "Vaccine Act" or "the Act"). Hereinafter, individual section references will be to 42 U.S.C. § 300aa of the Act.

[3] Pursuant to Section 300aa-13(a)(1), in order to reach my conclusion, I have considered the entire record including all of the medical records, statements, expert reports, and medical literature submitted by the parties. This opinion discusses the elements of the record I found most relevant to the outcome.

aggravated his underlying MS and caused a severe tumefactive MS when a milder, garden variety MS would more likely have occurred but for the vaccination.

## I. Procedural History

Petitioner timely filed his claim on November 29, 2017. *See* Petition. The case was assigned to my docket on November 30, 2017. *See* Notice of Assignment (ECF No. 4). After petitioner filed medical records, respondent filed a status report on August 16, 2018, indicating that the medical records were sufficiently complete for an analysis of his claim and requested a deadline to file a Rule 4(c) report. (ECF No. 14).

Respondent filed a Rule 4(c) report on October 4, 2018, in which respondent noted that following the DICP review of the case, the case was not appropriate for compensation under the terms of the Act. Respondent's Report ("Resp. Rept.") at 1 (ECF No. 16). An initial status conference was held on October 24, 2018, in which I ordered petitioner to file additional medical records and an expert report. *See* Scheduling Order at 2 (ECF No. 17). Petitioner filed additional medical records on January 11, 2019. Petitioner's Exhibit ("Pet. Ex.") 11-18 (ECF No. 20). On May 30, 2019, petitioner filed initial expert reports from Marcel Kinsbourne, M.D., a pediatric neurologist, and Vera Byers, M.D., Ph.D.[4] an immunologist. Pet. Ex. 25 (ECF No. 27); Pet. Ex. 48 (ECF No. 28). Petitioner also filed an expert report and a review letter from petitioner's treating neurologist, John Foley, M.D.[5] Pet. Ex. 62; Pet. Ex. 63 (ECF No. 29).

[4] The qualifications of Dr. Kinsbourne and Dr. Byers will not be enumerated in this ruling because the Court will not be considering their expert reports. Tr. 527-28. I held a status conference in October 2019 and explained to petitioner my concern with the expert reports filed at that time given the complexity of this case. Petitioner elected to retain new experts.

[5] Dr. Foley, petitioner's treating neurologist, filed two expert reports and testified in the entitlement hearing. Pet. Ex; 62; Pet. Ex. 63. He received his medical degree from the Medical College of Wisconsin and did a residency in neurology at the University of Utah Medical Center. Pet. Ex. 64 at 1. He is an expert in neurology and multiple sclerosis, and serves as The Director of the Rocky Mountain Multiple Sclerosis Clinic, which services approximately 4,200 patients a year. *Id.* at 2; *see also* Tr. 97. He is also the President of the Rocky Mountain MS Research Group and is an elected Fellow in the American Academy of Neurology. Pet. Ex. 64; Tr. 97-98. Dr. Foley himself sees 40-50 patients a week. Tr. 98. Petitioner offered Dr. Foley as an expert in the field of neurology with a special concentration in multiple sclerosis, and he was admitted as such. Tr. 100.

On September 20, 2019, respondent filed responsive expert reports from Thomas Forsthuber, M.D.,[6] and Subramaniam Sriram, M.D.[7] Resp. Ex. A (ECF No. 34); Resp. Ex. B (ECF No. 35). A Rule 5 status conference was held on October 23, 2019, and I ordered petitioner to submit supplemental expert reports to better address the nature of multiple sclerosis in the very rare tumefactive form,[8] the possible immune mechanisms, and the rapid timing of the aggravation seen in this case. *See* Scheduling Order (ECF No. 38). On July 30, 2020, petitioner filed an initial expert report from Lawrence Steinman, M.D.[9] Pet. Ex. 66 (ECF No. 50). On

[6] Dr. Forsthuber is a Professor of Immunology at the University of Texas at San Antonio and an Adjunct Professor of Pathology and Microbiology & Immunology at UT Health Sciences Center in San Antonio. Resp. Ex. C at 1 (ECF No. 37). He is board certified in Anatomical and Clinical Pathology. Tr. 437. He serves as the senior editor for expert review in *Clinical Immunology* and is on the editorial board of several medical and scientific journals. *Id.* Dr. Forsthuber graduated from medical school in Germany in 1986 and completed an internship in Medicine in 1987. Resp. Ex. C at 2. In 1993, Dr. Forsthuber passed the United States Medical Licensing Examinations in Basic Medical Sciences and Clinical Sciences. *Id.* In 1993, Dr. Forsthuber completed a postdoctoral fellowship in immunology at the University of California, Los Angeles. *Id.*; *see also* Tr. 434-35. He passed his licensing examination in 1995 and was issued a medical license in Ohio in 1996. Resp. Ex. C at 2. In 1998, he completed a residency in pathology at the University Hospitals Cleveland. *Id*. at 3. He testified that his research focuses on autoimmune diseases, particularly multiple sclerosis. Tr. 434-35. He also testified that he has published numerous papers related to MS and experimental autoimmune encephalomyelitis ("EAE"). Respondent offered Dr. Forsthuber as an expert in the field of immunology, and he was admitted as such. *Id*. at 439.

[7] Dr. Sriram is board certified in Internal Medicine and Neurology. Resp. Ex. B at 1. He is Professor of Experimental Neurology and Pathology, Microbiology, and Immunology at Vanderbilt University Medical Center. Resp. Ex. D at 2. He also serves as Director of the Multiple Sclerosis Clinic at Vanderbilt, where he takes care of over 1,200 patients in the outpatient clinic and 900 patients with MS. *Id*.; Tr. 318. He obtained a Bachelor of Medicine and a Bachelor of Surgery from the University of Madras in Madras, India. Resp. Ex. D at 1. He completed a residency in internal medicine at Wayne State University in 1976 and completed a residency in neurology at Stanford University in 1979, where he also served as chief resident. Resp. Ex. D at 1. He went on to complete a post-doctoral fellowship in neuroimmunology. *Id*. Dr. Sriram has published numerous peer-reviewed medical articles regarding demyelinating diseases of the central nervous system. *Id*. at 9-19. Dr. Sriram testified that he is board certified in internal medicine and neurology and continues to practice in the state of Tennessee. Tr. 317. Respondent offered Dr. Sriram as an expert in the field of neurology and multiple sclerosis, and he was admitted as such. Tr. 320.

[8] The respondent filed a paper by *Alghatani et al*, entitled *Tumefactive Demyelinating Lesions: A comprehensive review*. The article defined a tumefactive lesion as one that is an acute, large (greater than 2 cm), tumor-like demyelinating lesion in the CNS that may occur with surrounding edema, mass effect and ring enhancement. Hussein Algahtani et al., *Tumefactive demyelinating lesions: A comprehensive review*, 14 Multiple Sclerosis and Related Disorders 72, 72 (2017); Resp. Ex. A-1 at 1 (ECF No. 34). It is a rare variant of MS occurring in an estimated 1-3 per 100,000 cases of MS. Algahtani et al., *supra*, at 72; Resp. Ex A-1 at 1.

[9] Dr. Lawrence Steinman is a Professor in the Departments of Neurology and Neurological Sciences and Pediatrics and Genetics at Stanford University Medical Center. Pet. Ex. 67 at 1. Dr. Steinman received his undergraduate degree from Dartmouth College in 1968 and graduated from Harvard University Medical School in 1973. *Id*. He completed a residency in pediatrics in 1974 and a residency in pediatric and adult neurology in 1980, both at Stanford University Hospital. *Id.* Dr. Steinman is board certified in Psychiatry and Neurology. *Id*. at 2. Dr. Steinman has cared for adult and pediatric patients with various forms of inflammatory neuropathy, including, GBS, transverse myelitis, acute disseminated encephalomyelitis, neuromyelitis optica and multiple sclerosis. Pet. Ex. 66 at 1. Additionally, Dr. Steinman has served on multiple National Institute of Health's ("NIH") expert panels pertaining to vaccination, including the Advisory Committee on Pertussis Immunization and the Immunological Sciences Study Section. *Id*. at 2. Dr. Steinman was awarded the Charcot Prize for Lifetime Achievement in 2011 from the International Federation of MS Societies for his work in multiple sclerosis research, and he was elected to the National Academy of Sciences in 2015. Pet. Ex. 67 at 2. Dr. Steinman listed nearly 600 publications on his

September 21, 2020, respondent filed a supplemental expert report from Dr. Forsthuber. Resp. Ex. E (ECF No. 51).

I held a status conference on November 23, 2020 and ordered the parties to find a mutually agreeable time for an entitlement hearing in 2021 and to file supplemental reports from Dr. Steinman and Dr. Forsthuber. ECF No. 54. I also ordered petitioner to file updated medical records. *Id.* An Entitlement Hearing was set for October 27-29, 2021. *See* Hearing Order (ECF No. 55).

On February 16, 2021, petitioner filed a supplemental expert report from Dr. Steinman. Pet. Ex. 85 (ECF No. 60). Respondent filed a supplemental report from Dr. Forsthuber on March 31, 2021. Resp. Ex. F (ECF No. 61). In preparation for the entitlement hearing, petitioner filed prehearing submissions on September 1, 2021, and October 13, 2021, and respondent filed his prehearing submissions on September 27, 2021, and October 15. (ECF Nos. 66, 69, 76, 80).

An entitlement hearing was held on October 27-29, 2021 on Zoom with the Court sitting in Annapolis, Maryland, the petitioner and counsel in the Salt Lake City, Utah area, respondent's counsel in Washington, D.C., and experts appearing from Salt Lake City, Utah, Palo Alto, California, San Antonio, Texas and Nashville, Tennessee. Following the entitlement hearing, petitioner filed a post hearing brief on February 28, 2022, and respondent filed his post hearing brief on April 29, 2022. Pet. Post Hearing Brief (ECF No. 94); Resp. Post Hearing Brief (ECF No. 95). Petitioner filed a post hearing brief reply on June 9, 2022. Pet. Post Hearing Reply (ECF No. 100). Respondent filed a sur-reply on June 24, 2022. Resp. Sur-Reply (ECF No. 101). In petitioner's post hearing brief, a section was included to strike or otherwise discount Dr. Sriram's testimony based on his lack of credible testimony on his credentials.[10]

The matter is now ripe for adjudication.

## II. Legal Standard

*curriculum vitae*. *Id*. at 5-48. Additionally, Dr. Steinman has previously testified before the Vaccine Court as an expert in neurology and neuroimmunology. Tr. 202-03. Petitioner offered Dr. Steinman as an expert in neurology and neuroimmunology, particularly with regard to MS, and he was admitted as such. *Id.*at 203-04.

[10] Citing to *Contreras*, petitioner argues that Dr. Sriram misrepresented his membership as a Fellow in the American Academy of Neurology. *See* Pet. Post Hearing Brief at 9-12; *Contreras v. Sec'y of Health & Hum. Servs.*, 116 Fed. Cl. 472, 483 (Fed. Cl. 2014). Petitioner argues that the misrepresentation of his credentials calls into question the credibility of his entire testimony, as "it is conceivable that Dr. Sriram would do the same on the important matters regarding Mr. Gardner's medical records." Pet. Post Hearing Brief at 11-12. Respondent explained that Dr. Sriram is in fact "a member of two professional neurological associations, the American Academy of Neurology and the American Neurological Association." Resp. Post Hearing Brief at 23. Dr. Sriram is a member of the American Academy of Neurology and a Fellow of the American Neurological Association, his curriculum vitae contains that correct information, and Dr. Sriram misspoke at the hearing. *Id*. at 24. Petitioner's argument is completely unpersuasive in the present case, as Dr. Sriram is a qualified expert to opine on the neurological theory in this case. He is board-certified in Internal Medicine and Neurology. Resp. Ex. B at 1. He is Professor of Neurology and Microbiology and Immunology and head of the Multiple Sclerosis ("MS") Clinic at Vanderbilt Medical Center, where he takes care of over 1,200 patients in the outpatient clinic, and 900 patients with MS. *Id*. Tr. 313, 318. Therefore, he is qualified to opine on this case and his opinion will not be discounted based on a mere misstatement during the entitlement hearing.

The Vaccine Act was established to compensate vaccine-related injuries and deaths. § 300aa-10(a). "Congress designed the Vaccine Program to supplement the state law civil tort system as a simple, fair, and expeditious means for compensating vaccine-related injured persons. The Program was established to award 'vaccine-injured persons quickly, easily, and with certainty and generosity.'" *Rooks v. Sec'y of Health & Human Servs.,* 35 Fed. Cl. 1, 7 (1996) (quoting H.R. Rep. No. 908, at 3, *reprinted in* 1986 U.S.C.C.A.N. 6287, 6344).

A petitioner bears the burden of establishing his or her entitlement to compensation from the Vaccine Program. The burden of proof is by a preponderance of the evidence. § 300aa-13(a)(1). A petitioner may prevail by proving either that (1) the vaccinee suffered an injury listed on the Vaccine Injury Table with onset beginning within a corresponding time period following receipt of a corresponding vaccine (a "Table Injury"), for which causation is presumed or that (2) the vaccinee suffered an injury that was actually caused by a vaccine. §300aa-11(c)(1)(C)(i-ii). Under either method, however, the petitioner must also show that the vaccinee "suffered the residual effects or complications of the illness, disability, injury, or condition for more than six months after the administration of the vaccine." § 300aa-11(c)(1)(D)(i).

In the present case, petitioner does not allege a Table injury. Instead, petitioner alleges that he suffered an off-table significant aggravation of multiple sclerosis as a result of the flu vaccination on December 1, 2014. Pet. Post-Hearing Brief at 1. Thus, petitioner bears the burden of establishing actual causation.

The Vaccine Act defines significant aggravation as "any change for the worse in a preexisting condition which results in markedly greater disability, pain, or illness accompanied by substantial deterioration of health." § 300aa-33(4). The United States Court of Federal Claims established the governing six-part test for off-Table significant aggravations in *Loving*. Petitioner must prove by a preponderance of the evidence:

> (1) The person's condition prior to administration of the vaccine, (2) the person's current condition (or the condition following the vaccination if that is also pertinent), (3) whether the person's current condition constitutes a 'significant aggravation' of the person's condition prior to vaccination, (4) a medical theory causally connecting such a significantly worsened condition to the vaccination, (5) a logical sequence of cause and effect showing that the vaccination was the reason for the significant aggravation, and (6) a showing of a proximate temporal relationship between the vaccination and the significant aggravation.

*Loving v. Sec'y of Health & Human Servs.*, 86 Fed. Cl. 135, 144 (2009); *see also W.C. v. Sec'y of Health & Human Servs.*, 704 F.3d 1352, 1357 (Fed. Cir. 2013) (adopting this test as the proper legal standard for significant aggravation claims brought under the Vaccine Act). *Loving* prongs four, five, and six are derived from the Federal Circuit's test for off-Table actual causation cases. *See id.* at 143; *see also Althen v. Sec'y of Health & Human Servs.*, 418 F.3d 1274 (Fed. Cir. 2005).

The Federal Circuit clarified *Loving* prongs 3, 4, and 5 in *Sharpe*, further defining the requirements for petitioners to successfully demonstrate a cause-in-fact significant aggravation claim. *Sharpe v. Sec'y of Health & Human Servs.*, 964 F.3d 1072 (Fed. Cir. 2020). *Loving*

prong three only requires a comparison of a petitioner's current, post-vaccination condition with his pre-existing pre-vaccination condition. *Id.* at 1082. A petitioner is not required to demonstrate an expected outcome or that his post-vaccination condition was worse than such an expected outcome. *Id.* at 1081.

*Loving* prong four requires petitioner to provide only a "medical theory causally connecting [petitioner's] significantly worsened condition to the vaccination." *Id.* at 1083 (quoting *Loving*, 86 Fed. Cl. at 144). In other words, a petitioner is "required to present a medically plausible theory demonstrating that a vaccine 'can' cause a significant worsening" of the condition. *Id.* (citing *Pafford ex. rel. Pafford v. Sec'y of Health & Human Servs.*, 451 F.3d 1352, 1356-57 (Fed. Cir. 2006)). A petitioner may be able to establish a prima facie case under *Loving* prong four without eliminating a pre-existing condition as the cause of his significantly aggravated injury. *Id.* (citing *Walther v. Sec'y of Health & Human Servs.*, 485 F. 3d 1146, 1151 (Fed. Cir. 2007) (noting that "the government bears the burden of establishing alternative causation . . . once petitioner has established a prima facie case")).

*Loving* prong five requires a petitioner to show "a logical sequence of cause and effect showing that the vaccination was the reason for the significant aggravation." *Id.* at 1085 (quoting *Loving*, 86 Fed. Cl. at 144). In other words, petitioner must show that the vaccination "did" cause a worsening of petitioner's underlying disorder. *Id.* "The sequence of cause and effect is usually supported by facts derived from petitioner's medical records. *Althen*, 418 F.3d at 1478; *Andreu v. Sec'y of Health & Human Servs.*, 569 F.3d 1367, 1377 (Fed. Cir. 2009); *Capizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317, 1326 (Fed. Cir. 2006). In determining causation, a special master should consider the causation opinions of the treating providers as "treating physicians are likely to be in the best position to determine whether 'a logical sequence of cause and effect shows that the vaccination was the reason for the injury'" *Cappizano*, 440 F.3d at 1280.

In determining whether a petitioner is entitled to compensation, a special master must consider the entire record and is not bound by any particular piece of evidence. § 13(b)(1) (stating that a special master is not bound by any "diagnosis, conclusion, judgment, test result, report, or summary" contained in the record). Furthermore, a petitioner is not required to present medical literature or epidemiological evidence to establish any *Althen* prong. The special master essentially must weigh and evaluate opposing evidence in deciding whether a petitioner has met his or her burden of proof. *Andreu*, 569 F.3d at 1380; *see also Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1149 (Fed. Cir. 1992).

In Vaccine Act cases, expert testimony may be evaluated according to the factors for analyzing scientific reliability set forth in *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 594-96 (1993); *see also Cedillo v. Sec'y of Health & Human Servs.*, 617 F.3d 1328, 1339 (Fed. Cir. 2010) (citing *Terran v. Sec'y of Health & Human Servs.*, 195 F.3d 1302, 1316 (Fed. Cir. 1999). In Vaccine Program cases, these factors are used in the weighing of the scientific evidence actually proffered and heard. *Davis v. Sec'y of Health & Human Servs*., 94 Fed. Cl. 53, 66–67 (2010) ("uniquely in this Circuit, the *Daubert* factors have been employed also as an acceptable evidentiary-gauging tool with respect to persuasiveness of expert testimony already admitted"), *aff'd*, 420 F. App'x 973 (Fed. Cir. 2011). The flexible use of the *Daubert* factors to

determine the persuasiveness and/or reliability of expert testimony in Vaccine Program cases has routinely been upheld. *See, e.g.*, *Snyder v. Sec'y of Health & Human Servs.*, 88 Fed. Cl. 706, 742-45 (2009).

Where both sides offer expert testimony, a special master's decision may be "based on the credibility of the experts and the relative persuasiveness of their competing theories." *Broekelschen v. Sec'y of Health & Human Servs.*, 618 F.3d 1339, 1347 (Fed. Cir. 2010) (citing *Lampe v. Sec'y of Health & Human Servs.*, 219 F.3d 1357, 1362 (Fed. Cir. 2000)). However, nothing requires the acceptance of an expert's conclusion "connected to existing data only by the *ipse dixit* of the expert," especially if "there is simply too great an analytical gap between the data and the opinion proffered." *Snyder*, 88 Fed. Cl. at 743 (quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 146 (1997)). Weighing the relative persuasiveness of competing expert testimony based on a particular expert's credibility is part of the overall reliability analysis to which special masters must subject expert testimony in Vaccine Program cases. *Moberly v. Sec'y of Health & Hum. Servs.*, 592 F.3d 1315, 1325-26 (Fed. Cir. 2010) ("[a]ssessments as to the reliability of expert testimony often turn on credibility determinations"); *see also Porter v. Sec'y of Health & Human Servs.*, 663 F.3d 1242, 1250 (Fed. Cir. 2011) ("this court has unambiguously explained that special masters are expected to consider the credibility of expert witnesses in evaluating petitions for compensation under the Vaccine Act").

Close calls regarding causation must be resolved in favor of the petitioner. *Althen*, 418 F.3d at 1280 (holding that Congress created a system in which "close calls regarding causation are resolved in favor of injured claimants"); *Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 551 (Fed. Cir. 1994) ("If the evidence [on alternative cause] is seen in equipoise, then the government has failed in its burden of persuasion and compensation must be awarded.").

## III. Summary of Relevant Facts

### A. Prior Medical History before the December 1, 2014, Vaccination

On November 16, 2010, petitioner underwent an annual physical examination and petitioner's primary care physician ("PCP"), Dr. John Richards, wrote, "1. Last tetanus shot was more than 10 years ago. Did get a flu shot." Pet. Ex. 4 at 3. Petitioner testified during the entitlement hearing that he did not regularly get an annual flu shot, but that he had received one "four or five years, six years, [before this one] something like that." Tr. 59. After some discussion during the hearing, the undersigned stated that "… it's not completely definitive and, if that flu shot was the one that was primarily at issue in this case, we might look…for a more definitive record." *Id.* at 432. On further review of the record from the November 2010 physical, it appears that petitioner's PCP asked about the tetanus and flu vaccines and administered the tetanus vaccination. Pet. Ex. 4 at 3-4. As the flu shot is an annual shot, it is most likely that Mr. Gardner was would have also received the flu vaccine, if he had not yet received it that year. This would also be consistent with petitioner's recollection that he had received the flu vaccine several years before. *See* Tr. 59. As such, the undersigned has determined that "more likely than not [petitioner] did receive the flu shot in [2010]." *Id*. at 433.

Petitioner lives in Utah with his wife, Kim Gardner and their three children, and he holds both a bachelor's degree and master's degree in music. Pet. Affidavit ("Aff.") ¶ 3 (ECF No. 1). Mr. Gardner was 37 years old at the time of the 2014 vaccination. Pet. Ex. 4 at 7. Petitioner was working as a store manager for a local restaurant. Pet. Aff. ¶ 4. Other than as described below, petitioner had no disability prior to the vaccination. He testified that he was able to walk, run, play with his kids, engage in athletics, coach his children's sports teams, and lift things at work. Tr. 92-93.

On June 13, 2014, petitioner sought vision care from an optometrist at Riverton Family Eye care for changes to his vision, including "cloudy [or] dim" vision in his left eye. Pet. Ex. 2 at 1-6. Petitioner was diagnosed with rhegmatogenous retinal detachment[11] and ser-ous retinal detachment[12] and was referred to the University of Utah Moran Eye Center. *Id*. at 3. Dr. Trent Richards, an ophthalmologist at the Moran Eye Center, noted that petitioner continued to have blurred vision in his left eye that began on or about June 11, 2014 and progressed with "some pain when looking all the way to one side or the other." Pet. Ex. 3 at 1. Dr. Richards noted that petitioner had "been completely healthy," other than the blurry vision, and a dilated fundoscopic examination revealed left eye optic neuritis. *Id*. at 2.

On June 13, 2014, petitioner underwent an MRI of the brain which was "unremarkable with no stigmata of MS [but] consistent with left-sided optic neuritis." Pet. Ex. 3 at 3. On August 5, 2014, petitioner followed up with Dr. Judith Warner, a neuro-ophthalmologist at the Moran Eye Center. *Id.* at 8-9. Petitioner noted that there had been "some improvement of the vision" over the last six weeks. Dr. Warner personally reviewed his MRI and, in an addendum to her report, she noted that there was no evidence of demyelination but there was enhancement at the globe of the optic nerve. *Id.* Dr. Warner added that "his Aquaporin receptor antibody was negative, arguing against neuromyelitis optica…however, his ANA was positive with the Slc-70 also positive." *Id*. Petitioner elected to receive a course of IV steroids and was advised to follow up with Dr. Warner in one month. *Id*.

At his December 1, 2014 physical examination, petitioner told Dr. Richards, "in the last week his left leg, mostly on his foot but up to his lower left abdomen-feels almost like it has pins and needles. Comes and goes and nothing seems to make it worse. First time he felt it as a heat sensation on his anterior left thigh." Pet. Ex. 4 at 6. This is consistent with the history petitioner provided when he was admitted to Intermountain Medical Center on December 12, 2014, where he noted that, "around November of [2014], he began having parasthesias and numbness on his left leg" Pet. Ex. 11 at 8. At a later appointment on January 19, 2015, petitioner reported that he first noticed tingling in his left leg in August of 2014 and noticed cognitive changes, including difficulty with word finding, in September 2014. Pet. Ex. 6 at 2. However, there were no contemporaneous medical appointments between August and December 2014 discussing these

[11] Rhegmatogenous retinal detachment is the most common form of retinal detachment. *Types and Causes of Retinal Detachment*, National Eye Institute (Dec. 23, 2020), https://www nei.nih.gov/learn-about-eye-health/eye-conditions-and-diseases/retinal-detachment/types-and-causes-retinal-detachment.

[12] I can find no definition for the term "ser-ous retinal detachment," and, as such, conclude that it may be a typo for "serious." However, as mention of retinal detachment is not made again upon subsequent eye examinations by ophthalmologists at the University of Utah Moran Eye Center, I conclude that the optician's diagnosis of retinal tear, which he said was hard to see, was probably in error.

issues. During that time, petitioner continued to work a full-time job, was active with musical groups, and played actively with his children. Tr. 7-8.

**B. December 1, 2014 – December 9, 2014**

On December 1, 2014, petitioner presented to his PCP, Dr. John Richards, for a physical examination. Pet. Ex. 4 at 6. He went for a physical because his wife's company was providing incentives for employees and their families to have annual physicals. Tr. 40. Petitioner noted that "in the last week his left leg, mostly in his feet but up to his lower left abdomen – feels almost like it has pins and needles." Pet. Ex. 4 at 6. He reported that there was a "heat sensation on the anterior left thigh" when he first felt it and that the feeling comes and goes. *Id*. Petitioner also informed Dr. Richards that his uncle had recently been diagnosed with MS. *Id*. Petitioner received the flu vaccine at this appointment., *Id*. Dr. Richards performed a complete physical exam and noted full range of motion in ankles, knees, back, shoulders and elbows. Vision was good and extraocular muscles appeared normal. *Id.*

Mrs. Gardner testified that "between the December 1, visit and the December 10 visit, things started to get worse fast…[petitioner] had the weird muscle spasms, seizure thing, couldn't get warm, and then his leg started to get a lot worse…it started to go numb. He wasn't getting better." Tr. 15. Petitioner testified that he was in training at work and on his feet and his right leg stopped working "basically at my ankle. But it didn't stop me from going to work and standing on my feet. It didn't stop me from driving to work." Tr. 59. He testified that, after a few days, his right leg stopped responding, and he thought he might have had a pinched nerve. *Id.* On December 7, 2014, petitioner called into work and told them he was sick, as he was "feeling extremely cold and achy and [he] was barely able to use [his] right leg." Pet. Aff. ¶ 5. The progress notes from Wednesday, December 10, 2014, stated that "this last Monday he came in for his blood tests, when the [medical assistant] noticed he was having difficulty walking and set him up to see me today. His right leg has felt worse since Monday. While standing there he can hardly lift his right leg up. His memory has not been as good as it has been, and his brain feels 'foggy.' " Pet. Ex. 4 at 9. While there was some dispute as to whether the notation of "*this* last Monday," referred to the Monday before the December 10 appointment, December 8, or whether it referred to the original December 1, appointment, the undersigned concluded that the reference to "this last Monday" refers to December 8, 2014. Tr. 428. While there was no record of the blood work filed, the fact that Dr. Richards did a full physical exam, as described above, with no notation of trouble walking or weakness in the right leg on December 1, and that the December 10, note used the phrase "*this* last Monday" (emphasis added) when referring to the blood draw appointment when the medical assistant noticed that he was having trouble walking and set up the December 10 appointment, the context strongly supports the reference to the date of the blood draw as being December 8, 2014.

**C. December 10, 2014: return to PCP**

On December 10, 2014, ten (10) days after the flu vaccination, petitioner returned to Dr. Richards, reporting "tingling" in his left side and on the left side of his abdomen that "started a couple weeks ago and is still present." Pet. Ex. 4 at 9. He stated that his "skin was burning and…did not have any strength in [his] right leg and…had a sudden limp." Pet. Aff. ¶ 6.

Petitioner also noted "trouble walking" and that 2-3 days following the December 1, 2014 visit, his right leg "stopped working [and went] intensely numb, including his whole thigh and leg from the foot to the bottom of his right chest." Pet. Ex. 4 at 9. Petitioner noted his brain felt "foggy." *Id*. Dr. Richards found that petitioner's muscles in his right leg were significantly weaker than the left and he continued to have difficulty walking. *Id*. Mr. Gardner testified that he did not have any bowel or bladder problems until the day he went into the hospital. Tr. 61. None were noted in the medical record before that date.

**D. December 12, 2014: Intermountain Medical Center Emergency Room and admission to the hospital.**

On December 12, 2014, petitioner presented to Intermountain Medical Center Emergency Room when he lost his ability to walk and "completely lost the use of [his] right leg…[and] could not control [his] bladder or…bowels." Pet. Ex. 5 at 14; Pet. Aff. ¶ 7. He and his wife testified that he could not urinate at all on the morning of December 12. Petitioner's wife testified that she had to go into work that day, and, when she left, petitioner had crawled into the bathroom. Tr. 18. However, when she returned about an hour and a half later, petitioner was still in the floor and was unable to move. *Id.* Mrs. Gardner testified that, at this point, she became scared and dragged him down the steps and got him into the car to go to the hospital. *Id.* She decided to go straight to Intermountain Medical Center where there would be neurologists, as they had been having a hard time finding one since he saw Dr. Richards on December 10, 2014. *Id.* Petitioner was admitted to Intermountain Medical Center through the emergency room by neurologist Dr. Huan on December 12, 2014. Dr. Huan noted the past diagnosis of optic neuritis. She also noted that petitioner had some paresthesias and numbness on his left leg but no weakness around November. She described the f1u shot that he received 2 weeks prior to his presentation to the hospital. Pet. Ex. 17 at 1.

The neurologic examination revealed a left afferent pupillary defect. Both pupils were reactive, and petitioner had decreased visual field on the peripheral of the right eye and the left lower quadrant of the left eye. *Id.* at 2. The lower extremity exam showed that petitioner was "completely plegic with no movement at all in the right leg" and had normal movement in the left leg. *Id.* He had a T4-5 sensory level bilaterally, with elevated tone on the right. His strength in the arms was 5/5 with normal bulk. He had no sensory loss in the arms. *Id.* The diagnosis was "new onset myelopathy symptoms with right 1eg plegia and T5 sensory level along with new symptom of right likely right optic neuritis." *Id.* Petitioner also had "mild cognitive complaints" at that time. *Id.* Overall, Dr. Huan felt petitioner's symptoms were "suggestive of a demyelinating process." She ordered MRIs and other testing. *Id.*

After admission, petitioner underwent a brain MRI which revealed a peripherally enhancing intra-axial lesion centered in the left anterior temporal lobe, which was a "prominently T1 hypointense, T2 hyperintense, and somewhat heterogeneously FLAIR hyperintense intra-axial lesion." Pet. Ex. 17 at 12. The lesion demonstrated "prominent nearly complete peripheral enhancement, measuring 4.6 x 4.2 x 3.8 cm in AP, craniocaudal and transverse dimensions respectively." *Id.* A "very thin rim of surrounding parenchymal T2 and FLAIR hyperintense vasogenic edema" was demonstrated. *Id.* at 13. The radiologist interpreting the study noted that

"the appearance was most typical of active tumefactive demyelinating disease involvement." *Id.* There was age-appropriate cerebral volume. *Id*.

Petitioner also underwent a cervical spine MRI which revealed a prominent abnormal signal change and C6-T1 cord expansion with prominent enhancement at C7 to T1. Pet. Ex. 5 at 20-21.

The radiologist's impression was as follows:

> Given the prior left optic neuritis, current right optic neuritis, the large peripherally enhancing left anterior temporal lobe lesion, and the prominent fairly diffusely enhancing T2 [hyperintense] lesion in the cord at C7 and T1 on accompanying cervical and thoracic spine MRI exams and given previously negative workup for neuromyelitis optica and history of recent immunization, differential diagnosis would first include acute disseminating encephalomyelitis with transverse myelitis. [Neuromyelitis optica] would still be of consideration, as well as multiple sclerosis and viral myelitis.

*Id*. at 16. On December 12, 2014, petitioner was admitted with possible problems including "probable multiple sclerosis [and] history of optic neuritis." Pet. Ex. 5 at 113. The assessment included "nearly definite multiple sclerosis." *Id*. at 114. On December 14, 2014, petitioner underwent a lumbar puncture which showed two white blood cells, an elevated myelin basic protein, and no oligoclonal bands. *Id.* at 146, 161. Petitioner was discharged from the hospital to Intermountain Medical Rehabilitation Center on December 16, 2014, with diagnoses including multiple sclerosis, optic neuritis, and urinary retention. *Id*. at 161, 199. The discharge summary noted that petitioner had received a three-day course of intravenous steroids and had "no improvement." *Id*. at 161.

**E. Medical Records from December 2014 through 2016**

On December 22, 2014, petitioner underwent a follow-up brain and cervical spine MRI. Pet. Ex. 5 at 319-22. The brain MRI continued to demonstrate the inferior left temporal lobe T1 hypointense and T2 hyperintense lesions which measured approximately 4.4 x 4.2 x 2.8 cms. Since the prior exam, there was significantly decreased edema associated with this lesion. The enhancement had also minimally decreased particularly within the more posterior left temporal lobe. The radiologist indicated that these findings are consistent with tumefactive multiple sclerosis with mild treatment response. *Id.* at 320.

The brain MRI also showed a mild enhancement of the right infraorbital optic nerve, and a mild asymmetric atrophy of the right infraorbital optic nerve. *Id*. The cervical MRI showed an enhancing intramedullary lesion extending from the inferior endplate of C6 now extending through the mid-T2 vertebrae. *Id.* at 322. There was now a T2 hyperintense signal in the central gray matter pattern on the axial view. The lesion was slightly asymmetric to the right, similar to the prior MRI. *Id.* The findings were consistent with the progression of disease. *Id.* In his affidavit Mr. Gardner recounted that, during his hospitalization, he was seeing physical therapists, occupational therapists, speech pathologists, psychologists, neurologists and countless nurses. Aff. ¶ 8-11. While in rehabilitation, his condition worsened with essentially complete

paralysis of the right leg and new onset weakness in the left leg. Tr. 120-21. He also developed additional cognitive deficits and speech problems with continued bowel and bladder incontinence. *See* Pet. Ex. 327.

Petitioner was ultimately discharged from the Intermountain Medical Rehabilitation Center on January 9, 2015 and required stand-by assistance with activities of daily living at home ("ADLs"). He required assistance with complex tasks. Pet. Ex. 5 at 631-633. His discharge diagnoses were MS, lower extremity paraplegia, T4 sensory level, optic neuritis, cognitive deficits, urinary retention, constipation, and urinary tract infection. *Id*. at 631. Mrs. Gardner testified that upon discharge from the rehabilitation hospital "he [couldn't] move his legs…he [couldn't] remember anything." Tr. 22.

On January 19, 2015, petitioner presented to neurologist, Dr. John Foley, the Director of the Rocky Mountain Multiple Sclerosis Clinic. Pet. Ex. 6 at 1. Dr. Foley recorded an extensive history and noted the petitioner's optical symptoms began on June 11, 2014, when he was diagnosed with left optic neuritis. *Id*. By August 2014, petitioner noticed tingling in his left leg that lasted for several months, and by September 2014, petitioner started to notice cognitive changes such as "difficulty finding words." *Id*. at 1-2. Dr. Foley noted that, within a day or two of petitioner receiving the flu vaccination in question, he "became ill with nausea and flu-like symptoms requiring him to take a day off from work." *Id.* He called in sick on December 7, 2014 seven days after the vaccination. Pet. Aff. ¶ 5. Within 1 or 2 days more, petitioner was experiencing "increased cognitive difficulties, right blurred vision, persistent left leg numbness and paresthesia, and new right lower extremity weakness as well as urinary retention." Pet. Ex. 6 at 2. Dr. Foley conducted a full examination which showed that petitioner had mild weakness in his upper extremities, with a lower extremity strength of 0/5. *Id*. at 3. He noted that petitioner had received three days of IV steroids and a lumbar puncture that revealed no oligoclonal bands. The only abnormality was elevated myelin basic protein at 423. *Id.* at 2. While in rehab his symptoms worsened and in addition to his right lower extremity plegia, he began to note new left lower extremity weakness. *Id.* Dr. Foley's note reported significantly increased edema with minimally decreased enhancement of the left temporal lobe lesion. The spinal lesion showed some progression from C6-T1 to C6-T2 on the repeat scan with enhancement. *Id.* He received five days of plasmapheresis from December 27 – 31, 2014. and reported no improvement in leg function two days after completion. *Id.* He presented to the MS Clinic in a wheelchair, reporting some improvement in lower extremity movement in his toes and feet. His symptom profile over the last 30 days included severe bladder dysfunction requiring daily self cathing 4 times daily, sexual dysfunction, moderate fatigue, muscle weakness, muscle spasm, cognitive dysfunction, imbalance and bowel dysfunction including constipation and mild blurred vision with slurred speech occurring with increased fatigue. The hospital records documented a T4 sensory level. He reported normal visual acuity with persistent blurred left peripheral vision. *Id.* The receipt of the flu vaccine on December 1, was reported as part of the complete medical chronology. *Id.*

Dr. Foley ordered repeat MRIs of the brain, the cervical spine, and the thoracic spine, along with additional blood tests. *Id*. at 4. At that time, he concluded that petitioner demonstrated "subacute disseminated encephalomyelitis secondary to flu vaccine." *Id*.

Forty-five days after the initial MRIs petitioner underwent another MRI of the cervical spine and brain on January 26, 2015. Pet. Ex. 6 at 6. The cervical spine MRI revealed "mild fusiform cord lesion from C6-T2 with mild residual post-contrast enhancement but no cord expansion," which was similar to the December 2014 MRI. *Id*. The brain MRI showed "large left temporal lobe area of white matter T2 signal hyperintensity, with significant interval decrease in the degree of postcontrast enhancement, only mild residual, and with complete interval resolution of the previously demonstrated associated edema and mass effect, in fact, there now appears to be slight volume loss." *Id*. at 11-12. Additionally, "the previously suggested changes of the optic nerves are again noted but less prominent." *Id*. at 12.

Dr. Foley referred petitioner to Mountain Land Physical Therapy and Rehabilitation where he underwent a physical therapy evaluation for paraplegia due to "subacute disseminated encephalomyelitis." Pet. Ex. 7 at 8. Petitioner stated that in "February 2015, [he] was able to stand for short periods with a walker. For the first time in months, [he] was able to crawl upstairs to get to [his] bedroom and [he] was able to sleep in [his] own bed." Pet. Aff. ¶ 12. The examination "revealed decreased lower extremity strength, functional mobility and stability, which is consistent with impairments associated with MS." Pet. Ex. 7 at 9. Petitioner attended a total of 18 physical therapy sessions, ending on May 14, 2015, when the physical therapist noted that petitioner was "very functional in all his ADLs." *Id*. at 43.

Petitioner returned to Dr. Foley on March 9, 2015, and while he reported some improvement in his strength, he was only able to take steps with his walker, primarily used his wheelchair at home, and his gait remained restricted. Pet. Ex. 6 at 24. Dr. Foley noted that petitioner's "spinal cord disease clearly was related to his flu shot. This generated massive inflammation at the level of the lower cervical and upper thoracic spine with grossly enhancing lesion in the left temporal lobe consistent with ADEM post vac[cination] and recrudescence of probable multiple sclerosis." *Id*. at 24. Petitioner also reviewed all the written materials regarding Tysabri[13] and wished to proceed with the treatment. *Id*.

During a May 19, 2015, visit with Dr. Foley, he noted that while petitioner's "clinical status since beginning Tysabri [was] markedly improved," he tested positive for neutralizing antibodies and suffered from an allergic reaction to the infusion on April 6, 2015, and Dr. Foley concluded that "he is not a good candidate for retrial with Tysabri" on September 10, 2015. *Id*. at 28-30. During the physical exam, petitioner had full strength in all extremities and was able to ambulate 500 feet unassisted. *Id*. Due to his hospitalization and ongoing weakness petitioner was unable to "work from December 6, 2014, through May 2015," and he returned to work on May 27, 2015. Pet. Aff. ¶ 14. Petitioner testified that when he returned to work, he was "sensitive to heat," his eyesight felt "as if somebody smears Vaseline on eyeglasses," and he is "constantly in pain." Tr. 47-48. Further, he stated that he had other issues such as "keeping [his] balance," and feeling "tired." *Id*. at 48.

[13] Tysabri is an immunomodulator, which stops certain cells of the immune system from reaching the brain and spinal cord and causing damage. Tysabri treatment protocol includes a one hour infusion, once a month. (https://www.tysabri.com/).

On August 21, 2015, petitioner returned to Dr. Foley with complaints of "moderate fatigue…mild muscle spasms…mild memory/thought process deficits, mild imbalance, mild pain, moderate loss of vision…moderate blurred vision, mild bladder dysfunction, mild bowel dysfunction, mild sexual dysfunction, mild heat sensitivity." Pet. Ex. 6 at 33. The impression included "[relapsing remitting multiple sclerosis] RRMS," and recommendations to undergo "neurocognitive testing [and] ophthalmologist visit to delineate vision loss." *Id*. at 34.

Petitioner returned to Dr. Foley's office on August 26, 2015, reporting that two weeks earlier a relapse began with vision loss, and ongoing complaints of mild memory/thought process deficits, mild numbness and muscle spasms, mild loss of vision and vision loss, and mild bowel and bladder dysfunction. Pet. Ex. 6 at 36. Under "impression," it noted "RRMS with relapse including bilateral visual field defects," and the plan included "IVSM [intravenous Solu-Medrol] x 3 here starting today, [follow-up] with Dr. Warner[14] at Moran." *Id*. at 37. Petitioner was "forced to quit [his] job in August 2015 because of the inability to perform simple tasks, and because [he] had suddenly lost vision in both eyes." Pet. Aff. ¶ 16.

On September 9, 2015, petitioner returned to see Dr. Foley and reported that his "vision is getting worse." Pet. Ex. 6 at 46. The plan included adding two more days of IVSM via home health and the infusion clinic, and to follow up with Dr. Foley regarding disease-modifying therapy ("DMT") and a follow-up visit with Dr. Warner. *Id*. at 46-47. The next day petitioner presented to ophthalmologist, Dr. Jean Tabin, a colleague of Dr. Warner, at the Moran Eye Center with complaints of "decreased visual acuity." Pet. Ex. 3 at 15. Petitioner noted that his vision "has gone dark…and getting worse every day." *Id*. Dr. Tabin concluded that petitioner demonstrated "left homonymous bilateral field defects in visual field,[15] …relapsing remitting multiple sclerosis [history of] optic neuritis OS (left eye), possible parenchymal MS lesion." *Id*. at 17. Petitioner was also referred to "neuro-ophthalmology for a second opinion [and an] MRI." *Id*. The same day petitioner revisited with Dr. Foley to discuss "therapeutic options," because petitioner had "over the month of August [2015]…developed profound optic neuritis [in both eyes]." Pet. Ex. 6 at 49-50. Dr. Foley recommended against Tysabri based on the previous allergic reaction, and to try Tecfidera or a "trial of Rituxan off label as well." *Id*. at 50. Petitioner underwent a brain MRI on September 14, 2015, which found,

> The large areas of T2 signal hyperintensity and rim-like enhancement most consistent with new large areas of demyelinating disease involving the right parieto-occipital periventricular white matter and left frontal lobe with a small area of paramedian anterior left parietal vertex involvement as well. Findings consistent with active demyelination. Left temporal lesions has improved and shows no significant enhancement on today's study.

Pet. Ex. 8 at 1. Mr. Gardner also had a cervical-thoracic spine MRI performed on the same day. The radiologist noted that there was "ill-defined abnormal T2 and STIR hyperintensity in the

[14] Dr. Warner is a Neuro-opthalmologist with a practice at John A. Moran Eye Center at the University of Utah.

[15] Homonymous hemianopsia is defective vision or blindness in half of the visual field affecting the right halves or the left halves of the visual fields in both eyes. Dorland's Illustrated Medical Dictionary (33d ed. 2020).

lower cervical and upper thoracic cord from C6 to T2." *Id.* at 3. There was no abnormal contrast enhancement. The expansion seen in 2014 was no longer present and there is probably mild atrophy in the cord at these levels. *Id.*

On September 29, 2015, about ten months after the beginning of the major event, petitioner was again seen by Dr. Warner. Pet. Ex. 13 at 38. Dr. Warner noted a history of optic neuritis in petitioner's left eye, which began in June 2014, and in late July "sudden vision loss left eye, no eye pain, then right eye vision loss with no pain, then flare up of memory loss, speech problems, bowel problems, weakness in his legs but not as severe as in December." *Id*. at 39. She added that petitioner's "vision has not changed, cannot see with his left eye; vision [in] right eye came back but not to the baseline…overall getting better but very slow." *Id*.

Petitioner returned to Dr. Warner on November 10, 2015. She noted, "following aggressive treatment of his demyelinating disease his vision had improved to 20/20." Pet. Ex. 3 at 42. Dr. Warner noted that he had received "weekly IV methylprednisolone for 4 weeks." *Id*. Petitioner returned to Dr. Foley the next day, on November 11, 2015, and Dr. Foley's impression included "RRMS [Relapsing Remitting Multiple Sclerosis] on Tecfidera full dose 240 mg 1 po BID x 3[16] months and is feeling better. He received multiple doses of IVSM – 3 in August, 2 in September and 3 in October…continue Tecfidera and recheck blood tests in 3 months…schedule follow-up in 3 months." Pet. Ex. 6 at 52. On January 20, 2016, petitioner returned to Dr. Foley, who classified his condition as "relatively stable," and petitioner complained of "difficulty with visual acuity primarily in the lower half of his left eye visual field…[and] fairly significant cognitive decline." *Id*. at 59.

On March 15, 2016, petitioner returned for a follow-up to neuro-ophthalmologist Dr. Warner. Pet. Ex. 3 at 61. Dr. Warner noted that his vision had improved "slightly." He continued to have a defect on his left eye, but the homonymous hemianopia had nearly resolved. *Id*. Petitioner returned to Dr. Foley on July 27, 2016, with concerns about his short-term memory loss, with a note that the Tecfidera treatment was going well. Pet. Ex. 6 at 62.

**F. April 2017 – August 2021: Subsequent Course Including Follow-up imaging.**

Petitioner returned to Dr. Foley eight months later, on March 27, 2017, and reported no major relapses. Pet. Ex. 6 at 69. Further, Dr. Foley's impression remained "presumed MS," with the "possibility of ADEM appear[ing] less likely given the relapse." *Id*. at 71. Repeat brain and cervical spine MRIs were performed on April 3, 2017. Pet. Ex. 8 at 3-8. The brain MRI demonstrated improvement "since 9/14/2015. *Id*. A very large, tumefactive area of T2 and FLAIR signal abnormality in the left frontal lobe seen on 9/14/2015 has decreased significantly in size, previously measuring over 6 cm in AP diameter, and currently measuring about 4.1 cm." *Id*. at 6. The radiologist concluded, "findings presumably representing tumefactive plaque, with interval improvement," with "new increased signal intensity with associated volume loss in the anterior body of the corpus callosum which is felt to represent Wallerian degeneration related to the large left frontal lobe lesion." *Id*. at 7-8.

[16] This abbreviation means one by mouth. two times a day for three months.

The cervical spine MRI demonstrated "abnormal T2 and STIR hyperintensity in the lower cervical and upper thoracic cord [which] is again seen, but is quite ill-defined currently." *Id*. at. 4. Further, there was "no definite new signal abnormality nor abnormal contrast enhancement in the cervical cord." *Id*.

On April 5, 2018, petitioner had follow-up MRIs which were compared to the April 3, 2017 MRIs. *See* Pet. Ex. 18. The brain MRI demonstrated "mild cerebral atrophy for the age of 40 [and] multiple lesions compatible with multiple sclerosis." *Id*. at 2. The MRI of the cervical spine demonstrated "marked abnormal myelomalacia[17] of the cervical spinal cord beginning at the mid C6 level [with] thinning of the cervical spinal cord, the size of the lesions has increased when compared to prior examination of one June 2015." *Id*. at 4.

Later that month, on April 17, 2018, petitioner returned to Dr. Foley with complaints of worsening memory, "word finding difficulty, articulation…difficulty understanding instructions and recall of information. Learning new things can be difficult…episode of bilateral vision loss for several weeks, had to quit his job." Pet. Ex. 14 at 14. Petitioner continued "to have right sided warm, burning pain, constantly present, worse in evenings…generally weak [and] unable to build muscle bulk." *Id*.

At the time of filing of petitioner's affidavit, petitioner stated that he "had less endurance, less coordination…difficulty multitasking, and problems with both [his] short and long-term memory and [he had] trouble recalling words." Pet. Aff. ¶ 16.

Petitioner returned to Dr. Foley on July 10, 2018, where he recommended new MS medications including Ocrevus and Gilenya. Pet. Ex. 14 at 18. Dr. Foley noted that petitioner felt that "his neurological status is declining over time and recognizes the need for an effective DMT [disease modifying therapy]." *Id*. Petitioner returned to Dr. Foley for a follow-up on October 2, 2018 with complaints of "some weakness, cognitive dysfunction and fatigue [and] some bowel and bladder dysfunction." *Id*. at 21. Petitioner also noted that he recently tried weightlifting which "caused severe weakness and fatigue for several days…he does some light walking for exercise now." *Id*. Petitioner had started on Gilenya and "tolerated first dose well." *Id*.

On November 13, 2018, petitioner had a follow-up appointment with Dr. Foley. In the "History of Present Illness" section of the record, Dr. Foley wrote, "[ petitioner] returned to work in June 2015 but was unable to complete the job and in August to September 2015 he developed a large central scotomata bilaterally in his primary field of vision [and] was unable to continue work. He was on disability until September 2017 when Social Security felt he was able to return to work…he then attempted to return to work and in September 2017 noted onset of significant cognitive impairment." *Id*. He is now not working and disabled but not recognized by SS [social security]." *Id*. at 24. Under "Impression," Dr. Foley wrote:

> multiple sclerosis with significant exacerbation immediately following influenza vaccine…at the present time he is 100% disabled primarily at this point secondary to cognitive dysfunction…his symptomatology is directly related to the influenza vaccine he received. He likely did have a propensity for underlying multiple

[17] Myelomalacia is morbid softening of the spinal cord. Dorland's Illustrated Medical Dictionary (33d ed. 2020).

> sclerosis which was severely exacerbated by the influenza injection. He likely would've had a significantly more benign course to his MS had he not received the influenza vaccine.

*Id*. at 26.

On November 30, 2018, petitioner presented to Becky Bailey, PhD, for a neuropsychological examination. Pet. Ex. 95. Dr. Bailey noted that his "current MS symptoms included continued incontinence, chronic right-leg nerve pain, memory loss, speech dysfunction (e.g., word finding problems), and vision problems." *Id*. at 4. The diagnostic impression included "a number of areas of cognitive weakness (motor, processing speed, verbal fluency, auditory learning, multitasking), but one of the most disabling areas of concern is his loss of social skills and ability to read others." *Id*. at 8. Additionally, petitioner "demonstrates executive function difficulties involved in carrying out planned behavior quickly, effectively and efficiently as well as likely organic apathy." *Id*. Dr. Bailey also documented mild to moderate impairment in memory, significant depression and difficulty learning new things which likely resulted in the loss of a job at the VA which he had held for just four months. *Id*.

Petitioner returned to Dr. Foley on January 20, 2020, for "MS follow-up." Pet. Ex. 96 at 9. Petitioner continues to complain "of the right lower extremity weakness, difficulty with learning and memory and loss of vision involving the left eye lower half of his visual field…he remains 100% disabled. He also remains on Gilenya every other day." *Id*. Further, Dr. Foley noted that petitioner has "relatively stable symptomatology post ADEM with the cord involvement…he does have significant cognitive dysfunction, motor dysfunction, and hyperesthesia of the right leg together with persistent visual field loss OS [left eye]." *Id*. at 11.

Follow-up brain and cervical spine MRIs were conducted on August 26, 2020. *See* Pet. Ex. 96. The brain MRI demonstrated that the "demyelinating brain lesions have not significantly changed when compared to prior examination but continued to demonstrate demyelination in the left anterior frontal lobe, left anterior parietal lobe and right-side white matter." *Id*. at 43. The cervical spine MRI demonstrated "unchanged appearance of the demyelinating cervical spinal cord lesion without convincing new or enhancing lesions." *Id*. at 42. The cervical and thoracic MRI confirmed an unchanged long segment of chronic demyelination from C6 to T3-4. *Id at* 44. On September 22, 2020, petitioner returned to Dr. Foley and was noted to be "relatively stable…[but] continues to have difficulty with cognitive issues." *Id*. at 6. Dr. Foley wrote that petitioner has a "history of clear-cut optic neuritis followed by an acute disseminated encephalomyelitis-type event. He did have subsequent bilateral optic neuritis a few months later. It remains unclear whether this is residual ADEM or continuing MS." *Id*. at 8.

In March 2021, petitioner returned to Dr. Foley for a telehealth consultation with complaints of "right sided abdominal pain that moves down into his leg periodically…blurred vision and difficulty concentrating…vision loss in the left inferior lateral visual field." Pet. Ex. 96 at 4. Dr. Foley recommended remaining "off of DMT[18] for now [and] wait[in] to receive COVID-19 vaccine until more information is available." *Id*. at 5. In August 2021, petitioner returned to Dr. Foley, and he wrote that petitioner has "significant residual neurological

[18] DMT is disease modifying therapy.

compromise. due to his post axonal ADEM/MS." *Id*. at 1. Dr. Foley's impression was "significant residual from acute disseminated encephalomyelitis with extensive involvement in the cervical and thoracic spinal cord." *Id*. at 3.

Mrs. Gardner testified that her husband's "most common relapse symptoms include fatigue…hard time moving his legs…bowels are a constant issue." Tr. 32. At the hearing, petitioner testified that he was still experiencing leg and hip pain "every day," along with cognitive problems, memory problems, and brain fog. Tr. 81. He explained that brain fog means he "start[s] a sentence with the intention of including one particular word, and if I don't use the word quickly enough at the beginning of the sentence, by the time I get to where I'm going to place that word in that sentence, I've already forgotten what the word was in my own sentence." Tr. 81-82. He explained that his memory problems manifest as having issues "forming new memories." *Id*. at 82-83. While petitioner is engaged in conversations, he "can't recall the point of the conversation…[and] might close a conversation without realizing that the person I was talking to was about to say something." *Id*. at 84.

Petitioner explained that while he has not experienced any large-scale flares as he experienced in 2014-2015 he continues to have "small, short events, but nowhere near as extreme as the paralysis. The lack of putting words together, the lack of cognizance, all of that – all of those and the eyesight…you can stack all of those up, that's one really big event for me." Tr. 86.

## III. Analysis

### 1. *Loving* Prong One: Petitioner's condition before receiving the flu vaccine.

As detailed in the facts section above, petitioner appeared to be somewhat healthy before receiving the vaccine. He was a 37-year-old husband, and father of three, who was noted to have a "very healthy exam" during a physical on November 16, 2010. Pet. Ex. 16 at 1-8. At that appointment petitioner's PCP wrote, "1. Last tetanus shot was more than 10 years ago. Did get a flu shot." Pet. Ex. 4 at 3. He had only a few appointments in the intervening four years for allergies and sinus infections. *Id*.

At the December 1, 2014, appointment for a physical, petitioner reported to his PCP, Dr. Richards, that in the last week he had felt something almost like pins and needles mostly in the left foot but at times going up to the abdomen and also reported that he had had a recent left eye problem with optic nerve inflammation that was not helped by steroids. Otherwise, his physical examination was normal. His range of motion was good in his hips, knees, ankles, back, shoulder and elbows. His eye movement was good. eyes looked normal. All other systems were normal leaving the question of the pins and needles in the left leg. Pet. Ex. 16 at 9-10.

Petitioner's wife testified that, prior to the December events, petitioner was very active, spontaneous, and fun. He was in good health. He loved music and was in bands and composed for groups. He would run and chase the kids. He was tall and was into sports. When he started to have an eye problem in the summer, they had been working in the yard and she thought that he might have had allergies or something in his eye. Tr. 7-9. Dr. Steinman noted that petitioner was in relatively good health, he was "working, driving, being a great dad." Tr. 264.

The parties stipulated that "prior to his receipt of the flu vaccination, petitioner had a history of optic neuritis." Joint Submissions at 1 (ECF No. 80). The parties also stipulated that "prior to his receipt of the flu vaccination, petitioner likely had multiple sclerosis." *Id*.

In mid-June 2014, approximately 6 months prior to the flu vaccine in question, petitioner started to get blurry vision in the inferior aspect of his left eye. Pet. Ex. 3 at 1. After a comprehensive eye exam showed stage 2 nerve edema in his left eye, petitioner underwent a brain MRI on June 13, 2014, which showed optic nerve enhancement at the globe and "no stigmata of MS." Pet. Ex. 3 at 3. Additionally, petitioner had a negative Aquaporin receptor antibody, and positive ANA and Slc-70. *Id*. at 8. The experts agree that petitioner was diagnosed with optic neuritis in June 2014. *See* Pet. Ex. 25 at 1; Pet. Ex. 66 at 7; Resp. Ex. A at 4; Resp. Ex. B at 6. Dr. Foley testified that the "clinical examination by the neuro-ophthalmologist in June of 2014 clearly validated the concept that he had a real optic neuritis of the left eye." Tr. 119. Dr. Steinman testified "that [petitioner] had an episode of something called optic neuritis. It wasn't diagnosed at that time as multiple sclerosis, but with retrospective view, that may have been the first clinically apparent attack." Tr. 205-06.

Respondent points to various parts of the medical record that demonstrate "clinical symptoms of a demyelinating disease in the weeks before his December 1, 2014 vaccination." Resp. Post Hearing Brief at 27. These symptoms included pins and needles sensation in his left leg, and some trouble with word finding. *See* Pet. Ex. 4 at 1-2, 6; Pet. Ex. 10 at 2; Pet. Ex. 5 at 113. Dr. Foley further testified that, since Dr. Richards did not perform a basic neurological exam, he "can't absolutely say that …the pins and needles couldn't have been a prodrome of some kind of an MS attack." *Id*. at 120. During cross-examination, Dr. Steinman stated that "in hindsight" the cognitive difficulties and pins and needles sensation were "probably" symptoms of his yet undiagnosed MS. Tr. 297-98.

Further, Dr. Sriram testified that in his opinion petitioner had lesions in his cervical spine prior to vaccination, and that petitioner's "symptoms began a few days before his vaccination with the development of the sensory abnormalities on his left leg and this would indicate to me that he already had some inflammation in his spinal cord…[w]hether a vaccine can aggravate and perpetuate or expand an ongoing developing lesion is not something that is known to occur." Tr. 363-64. In response, Dr. Foley testified that it is "speculation" for Dr. Sriram to believe that petitioner's lesions in his brain and spine started in September or October in 2014 because "we don't have an MRI, and the data of intervening neurological events is at best extremely weak and driven primarily by the patient's self-report without examination confirmation." Tr. 599.

Taking into consideration the diagnosed optic neuritis, pins and needles sensation in petitioner's left leg and mild cognitive changes such as difficulty finding words, it is most likely that petitioner had MS before the vaccine at issue. However, other than the optic neuritis, petitioner had at most mild symptoms of tingling in the left leg prior to the vaccination. He was very active with his kids, with musical groups, working a full-time job and generally not experiencing symptoms of significant illness.

**2. *Loving* Prong Two: Petitioner's condition after receiving the vaccine.**

Based on the undersigned's review of the medical records set forth above, petitioner had sensory symptoms in the left foot and leg that came and went prior to his physical exam and vaccination on December 1, 2014. The record establishes that after the vaccination, petitioner's condition significantly worsened.

Within a couple of days after the vaccination petitioner developed flu like symptoms but did not initially have new neurological symptoms. He called in sick to work on December 7, because he felt achy and cold and was barely able to use his right leg. Up to that point, he was in training, was working on his feet, and was driving to work. Tr. 59. He testified that it took a few days and eventually his right leg stopped responding. He thought he might have had a pinched nerve. *Id.*

In his first expert report, Dr. Foley wrote, "within 1-2 days [petitioner] became ill with nausea and flu-like symptoms requiring him to take time off from work. He called in sick on December 7, [2014]. Within 1 or 2 more days after he experienced flu like symptoms he experienced increased cognitive difficulties, right blurred vision, persistent left leg numbness and paresthesia, and new right lower extremity weakness, as well as urinary retention." Pet. Ex. 62 at 1. He saw a medical assistant for a blood draw on December 8, 2014, and she noticed that he was having trouble walking. She scheduled him to see Dr. Richards again on December 10, 2014. At this appointment the right leg weakness and dysfunction was documented but he was still able to walk on his own. By December 12, he could not walk at all, and his wife had to drag him to the car to go to the hospital. Dr. Foley testified that petitioner's initial disease course in December 2014 "would be more typical of a real severe ADEM…sort of an atypical MS, because…he had a single major event." Tr. 115.

The parties stipulated that on December 10, 2014, "petitioner saw his primary care physician and reported that, 'two or three days' after his flu vaccination, his right leg 'stopped working' and that it went 'intensely numb," including the 'whole thigh and leg,' '[from] the foot to the bottom of the right chest." Joint Submission at 2.

As noted above, on December 1, 2014, the date of the vaccination, petitioner presented to Dr. Richards and reported that in the last week before his visit, his *left* leg from his feet to his abdomen had some "pins and needles" which came and went. Pet. Ex. 16 at 9 (emphasis added). Dr. Richards noted petitioner's prior optic neuritis diagnosis and that MS had been ruled out through the MRI. *Id.* Dr. Richards recorded the nerve irritation in petitioner's left leg and ordered the flu shot. *Id*. His physical was otherwise normal including full range of motion in all his joints.

When petitioner returned to Dr. Richards on December 10, 2014, due to "trouble walking," and tingling in his left leg that had "started a couple of weeks ago." Pet. Ex. 16 at 14. Further, petitioner noted that 2-3 days after the vaccination his *right* leg "stopped working [and] went intensely numb" from the bottom of his right chest to his foot. *Id*. Mrs. Gardner testified that "between the December 1, [2014] visit and the December 10, [2014] visit, things started to

get worse fast…he had weird muscle spasms, seizure thing, couldn't get warm, and then his leg started to get a lot worse, really, really fast." Tr. 15.

Petitioner presented to the emergency room ("ER") on December 12, 2014, when he lost his ability to walk because of a paralyzed right leg. Pet. Ex. 5 at 11. The admission note indicated that he was a good historian and reported the prior NMO diagnosis. It indicated that in about November he began noticing some paresthesias in his left leg but not weakness. About five days ago, he started having numbness in the left leg up to about T5 and had hyperesthesia and neuropathic pain in the left hip and torso. This developed into weakness to the point where his right leg was completely plegic today. He was unable to urinate, and a Foley catheter was placed. He also noticed some right eye pain with no loss of acuity. He came into the ER because of this progression of symptoms. Pet. Ex. 11 at 7. On physical exam, his right pupil was larger than the left (4 mm to 2.5 mm). He appeared to have a left afferent pupillary defect with reactivity in both eyes and some decrease in visual fields bilaterally. He did have an occasional misplaced word but was otherwise cognitively intact. *Id.* at 9-11.

On physical exam in the emergency room, petitioner was calm and articulate and able to describe his history in detail. He was able to ambulate with the right knee locked. On sensory exam, he complained of decreased sensation and hyperesthesia from his feet to the nipple level bilaterally. He was unable to lift his right leg against gravity at the knee and was unable to lift the right leg off the bed with hip flexion. There was marked weakness on the right leg with no dorsiflexion or plantar flexion. The left leg appeared normal. He had normal proprioception bilaterally and normal response to light touch but was severely hyperesthetic to pinprick on the right side as compared to the left. Pinprick on the right appeared to cause severe discomfort. He was oriented to person, place and time and his cognition was baseline. His recall for recent events appeared to be intact. Pet. Ex. 11 at 11. Based on the above presentation and examination, Dr. Chloe Huan, a neurologist, admitted him to the hospital for extensive evaluation, imaging and lab work. *Id*. at 12.

A brain MRI conducted on the same day revealed a previously unseen, enhancing tumefactive lesion in the left anterior temporal lobe, "measuring 4.6 x 4.2 x 3.8 cm…suggestive of acute tumefactive demyelinating disease involvement in this patient with brain MRI a few months ago reportedly negative for intracranial lesions." Pet. Ex. 17 at 12-13. The enhancement indicates that the lesion is new and active, and the location on the left side of the brain would correlate with right-sided symptoms, such as the new right-sided visual problems and lower extremity sensory loss experienced by petitioner. *Id*. at 15-16. Petitioner also underwent a cervical spine MRI which revealed prominent abnormal signal change and C6-T1 associated cord expansion with prominent enhancement at C7 to T1. Pet. Ex. 5 at 20-21. The radiologist noted:

> Given the prior left optic neuritis, current right optic neuritis, the large partially peripherally enhancing left anterior temporal lobe lesion, and the prominently enhancing T2 hyperintense lesion in the right dominant C6-T1 cord on accompanying cervical and thoracic spine MRI exams, and given previously negative workup for neuromyelitis optica (NMO) and history of recent immunization, differential diagnosis would first include acute disseminating

> encephalomyelitis (ADEM) with transverse myelitis. NMO would still be consideration, as well as multiple sclerosis and viral myelitis.

Pet. Ex 5 at 16. As noted by Dr. Foley, compared to the initial MRI performed in June 2014, the second round of MRIs performed on December 12, 2014, showed significant progression. Dr. Foley testified that the MRI images were,

> significantly worse than a standard presentation of multiple sclerosis…we didn't have spinal cord imaging, but we had brain imaging as of June of 2014 that revealed only optic neuritis and no lesion burden in the brain. So, over this time frame, to develop this kind of picture, I would really say was kind of more acutely reactive. The prior brain MRI was essentially normal except for the left optic neuritis.

Tr. 111-12. With this dramatic change in the MRIs of the brain and spinal cord, petitioner rapidly lost his ability to walk, he experienced changes in his cognition, such as difficulty finding words, and he also experienced blurriness in his right eye. Pet. Ex. 5 at 113. His physical examination on December 13, 2014, revealed decreased sensation to light touch from his left toe to T5 level, and his right leg was paralyzed. *Id*. Petitioner also demonstrated constipation and urinary retention. *Id*.

Mr. Gardner underwent a second MRI of the brain and cervical spine on December 22, which was compared to the first from December 12. The brain MRI showed a slight decrease in edema and enhancement from the prior scan consistent with tumefactive multiple sclerosis. It also showed enhancement of the right intra-orbital optic nerve with atrophy although a full optic scan was not done. Pet. Ex. 5 at 320. In contrast to the brain scan which showed some mild improvement, the cervical MRI documented an enhancing intramedullary lesion from the inferior endplate of C6 through the mid T2 vertebral body. This lesion resulted in expansion of the cervical cord. In addition, on axial view there was T2 hyperintensity in the central grey matter. The length and width of the cervical lesion increased significantly from the prior scan. *Id.* at 322.

Mr. Gardner was discharged to the Intermountain Rehab Center on December 16, 2014 where he remained until January 9, 2015. He received a three-day course of intravenous steroids without improvement. While in rehabilitation, his condition worsened with essentially complete paralysis of the right leg and new onset weakness in the left leg. He also developed additional cognitive deficits and speech problems with continued bowel and bladder incontinence. His diagnosis on discharge was multiple sclerosis, lower extremity paraplegia, T4 sensory level, optic neuritis, cognitive deficits, urinary retention, constipation, and urinary tract infection. Pet. Ex. 5 at 631.

Dr. Foley testified that these lesions did improve and the insult was largely monophasic except for an additional attack of optic neuritis with some mild MS symptoms in August 2015 which they treated at that time. Tr. 156. Dr. Foley put him on disease modifying therapy, initially Techfidera and then Ocrefus and finally Gilenya but he is now off MS medications.

Today, petitioner is dependent on his wife, and has not been able to be employed. Tr. 81. He continues to suffer from cognitive impairments, including word finding, brain fog and

memory problems. Tr. 81-83. Physically, he still experiences leg and hip pain, gets tired easily, cannot be intimate with his wife, and continues to suffer a blind spot "on the bottom left corner of [his] left eye," that it is "constantly blurry." *Id*. at 84. Additionally, he is sensitive to temperature changes and has experienced "small, short" flare-up events, but "nowhere near as extreme as the paralysis," experienced in December 2014. *Id*. at 86.

There is no question that petitioner's physical condition, and ability to function became significantly worse in the 10 to 12 days after the vaccination. His symptoms began with pins and needles on the left and some visual blurriness on the left at the time of vaccination, progressing to right leg paralysis, right optic neuritis, urinary retention, and bilateral paresthesias with what appeared to be increasing levels of cognitive deficits by December 12, 2014. His condition continued to worsen during his hospitalization and rehabilitation with significant deterioration in cognition and minimal improvement in physical function. All of the above required an extended hospitalization and rehabilitation. While he did not have an MRI immediately before his vaccination, he did have one in June 2014 that showed optic neuritis on the left side only but was otherwise normal with no evidence of MS. His symptoms at the time of vaccination were quite mild compared to those that developed by December 12, 2014. The MRIs done in response to his worsening condition showed dramatic, enhancing changes from the prior scan that appear to have occurred concurrently with the worsening of symptoms. The December MRIs also demonstrated a significant enhancing cervical/thoracic lesion as described above. This change in signs, symptoms and imaging satisfies *Loving* Prong Two.

**3. *Loving* Prong Three: Petitioner's change in condition constitutes a significant aggravation.**

As provided above, the Vaccine Act defines a significant aggravation as "any change for the worse in a preexisting condition which results in markedly greater disability, pain, or illness accompanied by substantial deterioration of health." § 300aa-33(4). The Vaccine Act requires only a comparison of a petitioner's current or post-vaccination condition with his pre-vaccination condition. *Sharpe v. Sec'y of Health & Hum. Servs.*, 964 F.3d 1072, 1078 (Fed. Cir. 2020).

When Dr. Foley was asked by the Court about the possibility of an inflammatory process occurring between the time of the flu vaccine on December 1, 2014, and the MRI on December 12, which showed large lesions and massive enhancement, he responded that "the timing of this obviously is critical, and absent any MRIs prior to the influenza injection, it is essentially impossible for us to know." Tr. 123-24. Dr. Foley testified that if you take from the point of injection, he nearly immediately notices some sort of reactive symptoms that suggest some systemic reaction to the flu shot. After a few days he starts to notice more neurological symptoms. Importantly, Dr. Foley explained that the spinal cord, especially the anterior spinal cord, where corticospinal tracts are located, is very small, less than a half dollar around, so lesion formation there is rapidly transmitted into clinical symptoms. *Id.* at 124. In petitioner's case, he only had some pins and needles paresthesias prior to the injection. Then, there are a couple of days where it seems that he reacted negatively to the flu shot but does not necessarily have worsened neurological symptoms. Then petitioner really starts to get much worse, to the point where his wife has to drag him down the stairs, taking an hour to get him into the car. *Id.* By December 12, 2014, he has right leg paralysis, severe weakness and bladder dysfunction. *Id.*

This evolution of symptoms correlates with him suffering tumefactive lesion formation with massive gadolinium enhancement suggestive of an active, open blood-brain barrier and blood cord barrier. Dr. Foley explained that an acute inflammatory lesion in the spinal cord that is gadolinium enhancing is going to manifest very, very rapidly as clinical symptoms. So, Dr. Foley stated that his inclination was that sometime in the first week after having the flu shot, he developed at least a spinal cord lesion that became nearly immediately symptomatic. *Id.* at 125.

When asked about the large tumefactive lesion, Dr. Foley testified that it was primarily in the temporal lobe into the frontal lobe on the left side, and would induce speech dysfunction, cognitive dysfunction, processing slowing, probably emotional abnormalities. He pointed to Mrs. Gardner's testimony that petitioner could hardly talk by the end of his admission and explained why more of petitioner's cognitive symptoms manifested during his rehabilitation stay. Specifically, Dr. Foley explained that cerebral lesions, especially those that originate in the white matter association area, "can take a little bit longer to manifest with clinical symptoms." *Id.* at 125. In addressing the timing, Dr. Foley stated that "in a hypothetical, I think it…it's possible that he was going into what would have been a low-grade kind of minimal relapse that really got exacerbated by the antigenic stimulus." *Id*. In agreement with Dr. Foley, Dr. Steinman wrote that "the [flu] vaccine massively accelerated the severity and extent of [petitioner's] disease, multiple sclerosis." Pet. Ex. 66 at 6.

Dr. Foley testified that in retrospect, the June 2014 optic neuritis diagnosis fulfilled the first McDonald[19] criteria, and the second, separate in time McDonald criteria was confirmed by the abnormal MRIs from December 12, 2014. Tr. 118. As a treating physician, Dr. Foley noted during a visit on January 19, 2015, that petitioner's "spinal cord disease clearly was related to his flu shot. This generated massive inflammation at the level of the lower cervical and upper thoracic spine together with a grossly enhancing lesion on the left temporal lobe consistent with ADEM post vax and recrudescence of probable multiple sclerosis." Pet. Ex. 6 at 24. Clinically, this was demonstrated in petitioner by December 12, 2014, when he lost his ability to walk. Pet. Ex. 5 at 14. Dr. Foley testified that this was an atypical presentation of MS, and, but for the prior optic neuritis, he would have called it frank ADEM. However, with the prior optic neuritis and no other evidence of brain lesions on the MRI from June 2014, Dr. Foley testified that "we have to describe it as an atypical MS with a single monophasic severe episode that was ADEM-like. Short of doing a biopsy of the brain that is the best that we can say." Tr. 117-18.

Referring to his explanation of the narrow spinal cord, Dr. Foley explained that "the tight binding correlate of expanding inflammation in a very small space, in a very critical space in the spinal cord will induce inability to walk and complete failure of bowel, bladder and sexual function very rapidly. There is not a lot of margin there." *Id.* at 143. His theory, he explained is "that the bulk of that lesion burden, gadolinium enhancement, and cord enlargement developed within the first few days after getting the influenza vaccine." Tr. 143.

[19] The McDonald criteria, last revised in 2017, are the most recent diagnostic criteria for multiple sclerosis combining clinical, imaging, and laboratory evidence. Alan J. Thompson, et al., *Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria*, 17 Lancet Neurol. 162, 162 (2018). The McDonald criteria for the diagnosis of MS is often referred to as disseminated in time and disseminated in space and can refer to separate episodes or radiologic findings. *Id.* Dr. Foley explained in his testimony, in the present case, the McDonald criteria for MS "is essentially two episodes, separated in space and time." Tr. 105.

Dr. Foley explained that the blood brain barrier is opened in response to an antigenic stimulus, and, "then circulating immune cells will rush into certain areas that are usually perivenular…and those inflammatory cells, if they aggregate in sufficient numbers will start to do a couple things." *Id.* at 121-22. One is that they can swell the spinal cord or the brain giving them a "swollen look with acute inflammation" as occurred in this case. *Id.* Dr. Foley testified that this swelling can put pressure on things like the corticospinal tract, which is the major motor tract going to the legs and it can compromise bowel and bladder function. *Id.* At the same time, the inflammatory aggregates also start exerting a negative effect on the neuronal pools which ultimately lead to atrophy seen in scans years later. *Id.* at 122. Dr. Foley noted that this was a monophasic event and that petitioner's MRIs have remained stable, but he testified that there is permanent compromise that is now manifest by myelomalacia or a shrinkage of the spinal cord related to the initial lesion burden during the monophasic event. *Id.* at 140-41. Petitioner also has disproportionate atrophy in the left temporal, frontal-temporal regions of the brain related to the lesion burden in the monophasic event. Dr. Foley indicated that Mr. Gardner will have permanent cognitive compromise, bowel, bladder and sexual compromise and when he gets fatigued, he still uses a cane. Tr. 140-41. Dr. Sriram testified that "these lesions were massively enhanced on December 12, [2014] and they weaned off by January 22, [2015], these large lesions…last longer than three to four months, so it's up a timeline for the beginning of this sometime in October, November. That's my best guess because these large lesions don't suddenly come up and suddenly disappear." Tr. 342.

Dr. Steinman, in agreement with Dr. Foley, stated that while it is possible that petitioner had lesions and MS prior to the vaccination, there is no way to definitively know. After receiving the vaccine, petitioner progressively developed significant new symptoms over the ensuing days and weeks. The increase in lesions seen in the December 12, 2014 MRIs correlated with worsening symptoms in the time period from December 1, 2014 to December 12, 2014. The increased symptoms and lesions represent a very substantial worsening of his condition, constituting a "significant aggravation." Tr. 205-06.

The cause of the worsening will be addressed below, under *Loving* prong five, considering whether the vaccine was more likely than not the cause of petitioner's condition becoming worse. However, there is no question that Mr. Gardner's signs and symptoms became much worse in the days to weeks after the vaccination than they were before. Petitioner therefore satisfies *Loving* prong three as having experienced a significant aggravation of his condition.

**4. *Loving* Prong Four (*Althen* Prong One): Petitioner has established a reliable and reputable theory of how the flu vaccine can cause the significant aggravation of multiple sclerosis.**

Under *Althen* prong one, the causation theory must relate to the injury alleged. Thus, a petitioner must provide a "reputable" medical or scientific explanation, demonstrating that the vaccine received *can cause* the type of injury alleged. *Pafford*, 451 F.3d at 1355-56. The theory must be based on a "sound and reliable medical or scientific explanation." *Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 548 (Fed. Cir. 1994). However, the theory need only be "legally probable, not medically or scientifically certain." *Id.* at 549. However, the theory still must be based on a "sound and reliable medical or scientific explanation." *Id.* at 548. The

Federal Circuit explained in *Althen* that "while [that petitioner's claim] involves the possible link between [tetanus toxoid] vaccination and central nervous system injury, *a sequence hitherto unproven in medicine*, the purpose of the Vaccine Act's preponderance standard is to allow the finding of causation in a field *bereft of complete and direct proof of how vaccines affect the human body." Althen*, 418 F.3d at 1280 (emphasis added).

### A. Petitioners' Experts' Opinions Regarding *Loving* Prong Four (*Althen* Prong One): Dr. Foley and Dr. Steinman

Dr. Foley, as the primary multiple sclerosis specialist treating Mr. Gardner, opined early in the course of treatment that he believed that the flu vaccine triggered this event. He explained that he is the Director of the Rocky Mountain Multiple Sclerosis Clinic, which takes care of about 4,200 patients a year from throughout the intermountain west, primarily with multiple sclerosis but also with other disorders such as ADEM and NMO. Tr. 97. He referred to the literature regarding vaccination and ADEM and indicated that the correlation with MS in the literature is less robust but that it is there. He said that he has no doubt on a clinical basis that it occurs, as he has taken care of multiple patients with MS occurring after vaccination. Tr. 145. As detailed above he explained his theory of antigenic stimulation that can arise from an infection or a vaccination. He indicated that onset or relapse happens more frequently from infection but does also occur after vaccination.

Dr. Steinman agreed with Dr. Foley as to the likelihood of vaccine causation and opined that there was homology between components of the 2014-2015 flu vaccine (received by petitioner) and components of myelin, in particular myelin oligodendrocyte glycoprotein or MOG that could give rise to molecular mimicry. Pet. Ex. 66. Dr. Steinman presented the theory of molecular mimicry, which explains how the introduction of the flu vaccine can cause an autoimmune response against myelin, and can cause significant aggravation of MS via an open blood-brain barrier. *See* Pet. Ex. 66; Pet. Ex. 85. He defined MOG as a molecule that is "almost exclusively expressed in the central nervous system…and it's come to be understood that it's one of the myelin antigens that is attacked in multiple sclerosis." Tr. 219. Dr. Steinman further testified that "the components of the influenza vaccine sensitized Mr. Gardner to MOG," because there exists "a molecular similarity between what's in the vaccine that he actually received and MOG itself."[20] Tr. 222. He opined that because the components of the flu vaccine that Mr. Gardner received in 2010 and the one that he received in 2014 were identical in relevant parts that it is likely that he had a rapid recall response to the 2014 vaccine. Tr. 251-53.

Dr. Steinman demonstrated his theory in three steps. Initially he utilized the BLAST database made available by the National Institute of Health to perform a BLAST search to look for any similarities between MOG and the components of the flu vaccine. Pet. Ex. 66 at 14 He chose MOG because it is a protein that is attacked in optic neuritis, MS, and ADEM. Tr. 223. The BLAST search lines up two proteins and asks where they align, which is step one. His

[20] Dean M. Wingerchuk & Brian G. Weinshenker, *Neuromyelitis optica spectrum disorder diagnostic criteria: Sensitivity and specificity are both important*, 23 Multiple Sclerosis J. 182, 182–84 (2017) [Pet. Ex. 93]; Maureen A. Mealy et al., *Vaccines and the association with relapses in patient with neuromyelitis optica spectrum disorder*, 23 Multiple Sclerosis & Related Disorders 78, 78–82 (2018) [Pet. Ex. 94].

BLAST search identified a sequence in which there were six out of eight amino acids in a row that were identical between MOG and the hemagglutinin in the influenza vaccine. Tr. 224. He testified that they concluded years ago, as published in *Scientific American*, that you need five out of twelve amino acids to be identical in a consecutive stretch, and you could get ADEM. Tr. 224. The BLAST search revealed "the sequence TGMEVGWY [which] has 6 of 8 amino acids in common between the flu vaccine and MOG which he testified is sufficient to cause clinically relevant neuroinflammation." Pet. Ex. 66 at 14. Dr. Steinman testified that this sequence similarity could be sufficient to cause aggravation of MS by molecular mimicry," and he opined that "the components of the influenza vaccine most likely sensitized Mr. Gardner to MOG [because of] a molecular similarity between what's inside the vaccine that he actually received and MOG itself." Tr. 221-22.

To support his theory, in his second step, Dr. Steinman discussed the *Gautam* papers, which were studies done in his lab at Stanford, and which demonstrated in two papers that as few as four native myelin basic protein amino acids were sufficient to stimulate myelin basic protein T cells and cause experimental autoimmune encephalitis ("EAE") in mice. EAE is a murine model of the human autoimmune disease, multiple sclerosis. Pet. Ex. 78; Pet. Ex. 79. In a subsequent paper published in 1998, Gautam and colleagues demonstrated that a *viral peptide* with limited homology to a self-peptide can induce clinical signs of EAE. They stated that T helper cells recognize foreign peptides bound to MHC class II molecules on antigen presenting cells and that their studies suggest that the exposure to pathogens may stimulate the self-reactive T cell repertoire such that it may trigger or exacerbate autoimmunity and cause paralysis in mice.[21] Pet. Ex 79 at 7. *Gautam* observed that *Wucherpfennig* and colleagues[22] provided strong evidence that peptides derived from certain viruses and bacteria could stimulate myelin basic protein specific T cell clones generated from MS patients. In the 1998 *Gautam* paper they demonstrated that EAE in mice can be induced by a cross-reactive viral peptide with limited homology and provided evidence for molecular mimicry triggered by a virus. *Id*. at 10. Dr. Steinman also cited to a paper by *Root-Bernstein*[23] that demonstrates molecular mimicry between Group A Streptococcus and or coxsackievirus and cardiomyocytes giving rise to rheumatic heart disease. *Root-Bernstein* used a similar BLAST search approach and accepted homology of five identical amino acids in ten to demonstrate molecular mimicry in this context. Pet. Ex. 88. In this step Dr. Steinman explained that *Gautam* and other papers showed "an autoimmune response can begin even if the molecular mimicry is not quite exact."[24] Pet. Ex. 66

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[21] Anand Gautam et al., *A viral Peptide with Limited Homology to a self peptide can induce clinical signs of experimental autoimmune encephalomyelitis*, 161 J. Immunology 60, 63 (1998).

[22] Kai Wucherpfennig, et al., *Recognition of the Immunodominant Myelin Basic Protein by Autoantibodies and HLA-DR2-restricted T Cell Clones from Multiple Sclerosis Patients*, 100 J. Clinical Investigation 1114 (1997). [Pet. Ex. 73].

[23] Robert Root-Bernsein, *Rethinking molecular mimicry in rheumatic heart disease and autoimmune myocarditis: laminin, collagen IV, CAR, and B1AR as initial targets of disease*, Frontiers in Pediatrics, Aug. 2014, at 1. [Pet. Ex. 88].

[24] Anand Gautam, et al., *A Polyalanine Peptide with only Five Native Myelin Basic Protein Residues Induces Autoimmune Encephalomyelitis*, 176 J. Exp. Med. 605, 605-09 (1992). [Pet. Ex. 77]; Anand Gautam et al., *Minimum structural requirements for peptide presentation by major histocompatibility complex class II molecules:*

at 9; Tr. 237. He referred to a paper by *Srinivasappa*[25] which demonstrated that almost 4% of antiviral monoclonal antibodies also reacted with self-proteins. Tr. 236. Dr. Steinman testified that complete identity of amino acids in the relevant peptide could give disease 80 percent of the time, and if you reduce the number of identities, you still get disease 40 percent of the time. Tr. 239. He emphasized that the experiments that they can do within the scope of the Vaccine Program are limited so that in proposing a theory based on peer reviewed literature, as he has here, he is showing that the vaccine with six of eight identities between it and MOG *could* cause disease. He acknowledged that the theory cannot be proven to a certainty, emphasizing that it is not possible to do specific experiments on the petitioners in vaccine cases. *Id.* at 241. However, these papers provide preponderant evidence of how cross reactivity between a vaccine and MOG can cause disease which is what he believes occurred in this case. *Id.*

In the third step in refining his molecular mimicry theory, Dr. Steinman referenced the Immune Epitope Database (IEDB) to determine if that sequence had been studied by others. The database is known as the Immune Epitope Database, which "catalogs experimental data on antibody and T cell epitopes studied in humans, non-human primates, and other animal species in the context of infectious diseases, allergy, autoimmunity, and transplantation." Pet. Ex. 66 at 14. Dr. Steinman also utilized the Influenza Research Database in the third filtration step. *Id*. at 14-15. He testified that "the third step is really illuminating," by asking if "anyone else report[ed] that TM sequence of eight amino acids, did anyone else study it, report it, publish it, and they did, and it's found in both the hemagglutinin of the influenza, and it's found in MOG." Tr. 225.

The assays for the sequences "included a large number of studies from peer reviewed publications…demonstrating viral neutralization, proliferation, and production of pathogenic cytokines in human cells." Pet. Ex. 66 at 18. Referencing the sequence alignments in his first expert report, Dr. Steinman testified that "the protein is broken up into peptide fragments, and these size peptide fragments can usually elicit an immune response, and they can actually – even a fragment as small as eight amino acids can elicit ADEM in an experimental animal." Tr. 232.

He explained that the TMEGY segment has been shown to be part of what humans actually respond to in the hemagglutinin of influenza and also that it has been studied in great detail in dissecting the nature of the immune response to MOG itself. Tr. 244-45. Dr. Steinman testified that the TGMVDGWY epitope is part of the hemagglutinin portion of the H1N1 component of the vaccine. He indicated that many papers found through the IEDB referenced the TMGV et cetera peptides we are looking at overlapping peptides of about 20 amino acids in length. He explained that in an ideal situation, experiments could be conducted where the length of the peptide was shortened repeatedly to see if it could be determined exactly what part of the peptide became the landing pad for the immune response in a patient. However, those types of experiments are not possible in the context of a vaccine case. Nevertheless, he found that the reference to this peptide in the IEDB supported his theory as it appears to be a region where the human immune response to influenza is targeted. *Id.* at 247. He also explained a chart of all of

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*Implications in induction of autoimmunity*, 91 Proceedings of the National Academy of Sciences 767 (1994). [Pet. Ex. 78]

[25] Javaraiah Srinivasappa, et al., *Molecular Mimicry: Frequency of Reactivity of Monoclonal Antiviral Antibodies with Normal Tissues*, 57 J. Virology 397 (1986).

the types of assays that were done to show that this is a region that is a landing pad in MOG. They used binding to HLA. They used B cell assays. They used a huge number of T cell assays to show that this region could elicit cytokines associated with multiple sclerosis, like gamma interferon and IL-17 and that it could cause experimental disease exacerbation. Tr. 249. As such, he found that the multiple references to this peptide in the IEDB helped support his theory as to how the vaccine *could* cause an aggravation of MS in Mr. Gardner.

On cross examination Dr. Steinman was asked about the e-values, or expect values, in the BLAST search step. Dr. Steinman explained that the e-values were designed to compare one entire protein to another, which have much longer stretches of amino acids. However, the immune system does not respond to entire proteins but rather to short stretches after the antigen is chopped up and presented to the immune system through the HLA molecule. It is these short stretches that are relevant to the immune system response to the H1N1 molecules and to MOG. Tr. at 288. Dr. Steinman testified "that's why I go through the two other steps of the filtration…first [to] look for any alignment." *Id.* at 287. He explained that "the reason BLAST started out [was] they wanted to know how similar one protein was to another. I'm not interested in the whole protein. I'm interested in defined regions because the immune system doesn't scan whole proteins. It chops up the protein using enzymes called proteases and chops it up into short amino acid sequences that then bind to HLA molecules." *Id*. at 288. Further, he testified that "I don't care about the expect value number, because that's not what the immune system cares about." *Id*. at 289. While Dr. Steinman testified that he is "completely aware of the expect values," he stated that he doesn't "think they're relevant to the analysis that I'm doing for what the immune system might be interested in." *Id*. at 288. There is little doubt but that foreign pathogens such as the flu virus are chopped up inside cells and short segments are presented to the immune system on MHC molecules on the surface of the cell. Antibodies and T cells recognize short segments of pathogens called epitopes and mount the immune defense based upon that recognition. Dr. Steinman's theory is based upon recognition of short segments or epitopes that have similarity between the ingredients in the vaccine and components of myelin such as MOG. He argued that the *Gautam* and *Root Bernstein* papers among others demonstrate that short segments have been shown to cause clinically meaningful disease and that the third step in his filtration system has demonstrated that others are interested in the segment that he identified as being likely to be immunologically significant in causing cross reactivity and aggravation of MS.

Regarding onset, Dr. Steinman agreed that petitioner suffered some symptoms within two to three days following the flu vaccine at issue. Tr. 250. He testified that the onset is particularly appropriate "if this were a recall response." *Id*. at 251. Dr. Steinman testified that a corollary to the recall response to petitioner is an injection of tuberculin, and that "if you actually had been exposed to tuberculin or had tuberculosis, that arm might look red and angry in 24 hours or less."[26] *Id.* at 251. He further testified that "recall immunity is very fast…sometimes the very fast response is not necessarily in a neutralizing antibody. It's in a memory killer T cell." *Id.* at 252.

[26] Tiromourougane Serane, et al., *Tuberculin Test Can Be Read After 24 Hours in Adolescent Children*, 60 J. Tropical Pediatrics 157 (2014) [Pet. Ex. 105]; Lin Fan, et al., *Variation of Mycobacterium tuberculosis Antigen-Specific IFN-γ and IL-17 Responses in Tuberculin Skin Test (TST)-Positive Human Subjects*, PloS One, Aug. 2012. [Pet. Ex. 106]; T. Kardjito & J.M. Grange, *Immunological and Clinical Features of Smear-Positive Pulmonary Tuberculosis in East Java*, 61 Tuberculosis, 231 (1980. [Pet. Ex. 107].

Referring to petitioner's medical records from November 2010, Dr. Steinman noted that Mr. Gardner had received the flu vaccine available in that year as I have concluded was most likely to be the case. He explained that the flu vaccine in 2010 contained the same HIN1 virus as the 2014 flu vaccine, which is sufficient to mount a rapid recall response. Tr. 253. Thus, Dr. Steinman concluded that there is sufficient identity between the influenza vaccine administered to petitioner in 2014 and the one he received in 2010, with structural similarities known to be targeted in MS to cause a faster recall response. Pet. Ex. 66 at 20. Dr. Foley testified that the enhancing lesions suggest a very open blood brain barrier at the time of vaccination which together with the concept of a recall response helps to explain the rapid onset of the aggravation of Mr. Gardner's disease. Dr. Foley testified that this type of response is-

> usually due to a stimulus of some sort, and what happens then is circulating immune cells will rush into certain areas that are usually perivenular [around a vein]…those inflammatory cells, if they aggregate in sufficient numbers…can swell the spinal cord or the brain…and the swelling can actually put pressure on things like the corticospinal tract which is your major motor tract going to the legs, and it can compromise bowel and bladder function.

Tr. 121-22.

### B. Respondent's Experts' Opinions Regarding *Loving* Prong Four (*Althen* Prong One): Dr. Sriram and Dr. Forsthuber

Dr. Forsthuber argued that the three-step filtration system Dr. Steinman used to demonstrate a theory that the flu vaccine could aggravate petitioner's MS is not reliable. Tr. 440.

Regarding the first step, Dr. Forsthuber testified that a BLAST search is a "bioinformatics approach to enter sequences which are either nucleotide sequences, meaning DNA or RNA, or amino acid sequences from proteins in a software package that's available via the National Institutes of Health." Tr. 441. He testified that the "BLAST was not designed as an immunological tool…BLAST only shows you whether there is a certain level of similarity in nucleotides or amino acids between your protein that you're interested in versus other proteins." *Id.* at 442.

Dr. Forsthuber argues that even if the BLAST step were an effective tool for identifying immunological relationships, the comparison between MOG and the flu vaccine is not significant because of their high e-values. Tr. 447. He explained that e-values are used to determine whether or not the match is meaningful. *Id*. at 444-45. A meaningful e-value is lower and a non-meaningful e-value is higher. *Id*. Dr. Forsthuber relies on the National Institute of Health criteria that any e-value is significant if it is less than or equal to 0.00001. *Id*. at 445. He said that the e-value for the comparison between the 2009 California influenza strain and MOG was 0.1. *Id.* at 447. He said he would never consider this as a similarity. *Id.* at 449.

He pointed to an article by *Trost et al.* which addressed bacterial sequences, suggesting that about 50,000 perfect sequences, each 9 amino acids long, are shared between 40 bacterial

proteomes and about one third of the human proteome.[27] The *Trost* article concluded that "our past and present data tend to exclude a causal mechanistic role for molecular mimicry in the genesis of autoimmunity." Resp. Ex. E-11 at 3.

Dr. Forsthuber opined that "the 'sequence similarity' for which Dr. Steinman claims molecular mimicry is only 3 amino acids interspersed by two not matching amino acids and then another three amino acids and not 8 amino acids which perfectly match." Tr. 451. (Dr. Steinman testified that the match he referenced was 6 of 8 amino acids that matched not 8 of 8 and that 6 of 8 can be enough to induce autoimmunity) Referring to the *Trost* article, Dr. Forsthuber testified that the "sequence similarity between bacteria and humans is frequent." Tr. 450. The authors in *Trost*, "examined for amino acid sequence similarity" between bacterial proteomes and the human proteome. Resp. Ex. E-11 at 1. The article found that "the bacteria-versus-human nonamer (nine amino acids) overlap is numerically defined by 47,610 total perfect matches disseminated through 10,701 human proteins." *Id*. Dr. Forsthuber explained that "these short amino acid similarities, even up to nine amino acids, are so frequent that it is conceptually very difficult to say that these short sequences are causing molecular mimicry." Tr. 450-51. Dr. Forsthuber concluded that this research undermines any possible role of molecular mimicry and that if it did have a role due to the extensive overlap, the incidence of autoimmunity should occur at a rate of 100 percent. *Id.* at 450-52. The Court asked Dr. Forsthuber to clarify exactly what the paper said, and Dr. Forsthuber responded that "the paper is more careful…[and] they're a little more cautious in their wording," regarding the possible matches needed to induce autoimmunity via molecular mimicry. Tr. 451-52. Further, Dr. Forsthuber argued that even if MOG is significant in multiple sclerosis, the amino acid sequence outlined by Dr. Steinman does not include matches for the essential positions of the MOG sequence that researchers have identified as critical for T cell responses and induction of an autoimmune disease. Resp. Post Hearing Brief; Tr. 455.

Regarding the second step, Dr. Forsthuber distinguished the approach used by Dr. Steinman and the papers he relied on by *Gautam.* Tr. 461-62. Dr. Forsthuber argued that, in order to rely on the *Gautam* papers, two facts are necessary to induce an immune response. The first is that the relevant peptide must bind to the MHC molecule, and secondly the T cells need specific amino acids in defined positions in order to react. *Id.* at 463-64. He further argued that Dr. Steinman does not know "definitively" exactly which of the six out of eight amino acids would be correct to induce a reaction, and, therefore, without that knowledge his theory is pure speculation. He later testified that the positions of amino acids "are actually not so critical, but what's in [the] position is critical…if the wrong amino acid is in the wrong position, you'll lose binding." *Id.* at 473. Further, "you can't predict just by looking at the sequence…it's impossible to *predict* what would bind. It's simply not possible…the chances that you're getting a wrong amino acid in the right position are much higher than getting by chance the right amino acid in the right position." *Id*. at 474 (emphasis added).

Regarding the third step, Dr. Forsthuber stated that the influenza research database and the immune epitope database are not two distinct steps because they are pulling the same data. Tr. 480. He explained, as did Dr. Steinman, that the IEDB database "provides researchers with

[27] Brett Trost, et al., *Bacterial peptides are intensively present throughout the human proteome*, 1 Self/Nonself 71 (2010). [Resp. Ex. E-11].

the tools to search whether epitopes…that they have identified in their research…have been reported by someone else. It gives you some tools where you can try to identify epitopes on your own that could potentially induce T cell responses or B cell responses." *Id*. Dr. Forsthuber then explained that the exact eight amino acid sequence identified by Dr. Steinman was not present by itself in the database, therefore no one "has ever found immune reactivity to those two eight amino acid sequences." *Id*. at 481-82. It is part of a longer sequence between positions 35 and 55 in mice which is often looked at by researchers. Citing to a paper by *Mendel*, Dr. Forsthuber testified that "just because a sequence is listed in IEDB does not mean that actually your sequences that is part of a larger sequence has meaning in inducing immune responses."[28] Tr. 486; Resp. Ex. E-6. Dr. Forsthuber explained that while the sequences identified by Dr. Steinman are in mouse models, the *Mendel* paper indicated that positions 40-48 are the relevant positions for inducing disease in mice, and this sequence does not match Dr. Steinman's alleged mimics. Tr. 486; Resp. Ex. E at 24.

He additionally testified that "the reports on the influenza epitopes are after infection," not after vaccination. Tr. 492. He stated that when "we immunize an animal or a human being with a protein, the immune system only responds to a few regions on this protein…the immune system doesn't respond to…every sequence in this protein, just against a few of those regions. And during infection, typically more epitopes are induced as compared to vaccination." *Id*. at 493. Therefore, Dr. Forsthuber argued that the alleged mimic identified by Dr. Steinman is not capable of inducing inflammation or disease.

Dr. Forsthuber argued that Dr. Steinman's theory is not supported in the scientific community and has not been subjected to peer review. Dr. Steinman points to the *Root-Bernstein* paper as evidence that scientists have used similar methods. Dr. Forsthuber testified that the *Root-Bernstein* paper uses a different approach in which the authors conduct "BLAST searches and LALIGN searches," and if the sequences match 60% of the time, it is significant, if it is less then it is a meaningless comparison. Tr. 497-498. Therefore, Dr. Forsthuber argued that *Root-Bernstein* "would have discarded this result and these sequences as being meaningless, based on simply that they fall below the Blast significance standard." Tr. 498.

Dr. Sriram argued that the flu vaccine has not been shown to cause or aggravate MS, and it also doesn't impact the production of MOG antibodies. He discussed multiple studies that examined the relationship between vaccination and the clinical or radiological worsening of an autoimmune condition, and said that they have failed to substantiate these claims. Resp. Ex. B at 7. He cited to a paper by *Hapfelmeier et al.*, which looked to see "whether the onset of MS, which is often a relapse, is preceded by a vaccination, and they looked at three different autoimmune diseases, MS, Crohn's Disease, and psoriasis."[29] Tr. 380. The study used a cohort of 12,000 patients with MS and found that vaccines were not associated with a higher likelihood of

[28] Itzhak Mendel et al., *Delineation of the minimal encephalitogenic epitope within the immunodominant region of myelin oligodendrocyte glycoprotein: diverse V beta gene usage by T cells recognizing the core epitope encephalitogenic for T cell receptor V beta b and T cell receptor V beta a H-2b mice*, 26 Eur. J Immunol. 2470 (1996). [Resp. Ex. E-6].

[29] Alexander Hapfelmeier et al., *A large case-control study on vaccination as risk factor for multiple sclerosis*, 93 Neurology, 908 (2019). [Resp. Ex. B-3].

an MS diagnosis." *Id*. at 381. Dr. Sriram explained that the study found that vaccines "protected, to some degree…the risk of MS, to the extent that it was reducing the onset of an MS event." *Id*. He also cited to a study by *Confavreux*, which studied the relationship between multiple vaccines and risk of MS relapse.[30] The study concluded that "there was no increase in the specific risk of relapse associated with tetanus, hepatitis B, or influenza vaccination." *Id*. at 1. A review by *Mailand* similarly concluded after a systematic literature review that there is "no change in risk of developing [MS] after vaccination against…seasonal influenza."[31] Tr. 388; Resp. Ex. B-1.

Dr. Sriram acknowledged that the possible protective effect was likely because the vaccine reduced the likelihood of the patient developing the wild infection, in this case influenza which he agreed can trigger an MS attack. Tr. 383-84. He also agreed that these studies did not rule out rare occurrences of MS after vaccination. He said there is no way to rule out rare events. Tr. 395-86.

Dr. Forsthuber testified that there has been extensive research on whether the flu vaccine case cause or aggravate experimental autoimmune encephalomyelitis ("EAE") in mice and stated that the research demonstrated that the flu vaccine has no effect on the course of EAE in mice. Tr. 499; Resp. Ex. F-3. Dr. Forsthuber cited to an article by *Stojkovic*, which found increased anti-MOG antibodies detected in all of the mice with EAE, and no difference in anti-MOG antibodies found between vaccinated and unvaccinated mice with EAE. *Id.* Dr. Forsthuber testified that since MOG antibodies are the basis of Dr. Steinman's theory, this study undermines his theory. Dr. Forsthuber testified that the mice models in EAE are more like ADEM models, but we call it MS and the model doesn't perfectly replicate everything that happens in humans. So, we know there are limitations. Tr. 498.

### C. Discussion and Conclusion Regarding *Loving* Prong Four (*Althen* Prong One):

Under *Althen* prong one, petitioner must set forth a medical theory explaining how the vaccine could have caused his significant aggravation. *Andreu*, 569 F.3d 1367, 1375 (Fed. Cir. 2009); *Pafford*, 451 F.3d at 1355-56. This prong requires petitioner to make an evidentiary showing that the vaccine "can" cause the injury alleged. *Pafford*, 451 F.3d at 1356.

The causation theory must relate to the injury alleged. The petitioner must provide a sound and reliable medical or scientific explanation that pertains specifically to this case, although the explanation need only be "legally probable, not medically or scientifically certain." *Knudsen*, 35 F.3d at 548-49. Recently, in *Kottenstette*, the Federal Circuit reiterated that proof of causation does not "require identification and proof of specific biological mechanisms[.]" *Kottenstette v. Sec'y of Health & Hum. Servs.,* 861 F. App'x 433, 440-41(Fed. Cir. 2021) (citing *Knudsen v. Sec'y of Health & Hum. Servs.*, 35 F.3d 543, 549 (Fed. Cir. 1994)). Causation "can be found in vaccine cases…without detailed medical and scientific exposition of the biological

[30] Christian Confavreux et al., *Vaccinations and the risk of relapse in multiple sclerosis,* 344 The New England Journal of Medicine 319 (2001). [Resp. Ex. B-2].

[31] Mia Mailand & Jette Fredriksen, *Vaccines and Multiple Sclerosis: A Systematic Review*, 264 J. Neurol. 1035 (2016). [Resp. Ex. B-1].

mechanisms." *Knudsen,* 35 F.3d 543, 548-49 (Fed. Cir. 1994). It is not necessary for a petitioner to point to conclusive evidence in the medical literature linking a vaccine to the petitioner's injury, as long as the petitioner can show by a preponderance of evidence that there is a causal relationship between the vaccine and the injury, whatever the details of the mechanism may be. *Moberly v. Sec'y of Health & Hum. Servs.*, 592 F.3d 1315, 1325 (Fed. Cir. 2010).

Petitioner's expert, Dr. Steinman, opined that there is homology between components of the flu vaccine and components of myelin in the human body. Pet. Ex. 66. As required by *Althen* and other cases in the program, he presented a *theory* of molecular mimicry and recall response, which explains how the introduction of the flu vaccine can cause an autoimmune response against myelin, which can cause significant aggravation of MS beginning within 2-3 days. Pet. Ex. 66. He concluded that there is sufficient structural similarity between the influenza vaccine, particularly the H1N1 component administered to petitioner, with components of myelin in the central nervous system, known to be targeted in optic neuritis, MS, transverse myelitis, and ADEM." Pet. Ex. 66 at 20. Further, Dr. Foley opined that the vaccine worked as an antigenic stimulus which can open the blood brain barrier or, in this case, stimulated immune cells to rush into the central nervous system via an open blood-brain barrier. He testified that these cells are usually perivenular and if they aggregate in sufficient numbers, they can cause swelling in the brain or the spinal cord with acute inflammation as occurred in this case. The swelling can put pressure on things like the cortico-spinal tract which is the major motor tract going to the legs and can affect bowel and bladder function as well. Tr. 121-22. Dr. Steinman testified that "recall immunity is very fast…sometimes the very fast response is not necessarily in a neutralizing antibody. It's in a memory killer T cell." Tr. 252.

Dr. Steinman researched his theory by running BLAST searches to look for homologies between the components of the Flu vaccine and MOG, "a nervous system protein in the myelin sheath known to be targeted in ADEM…optic neuritis, transverse myelitis and MS." Pet. Ex. 66 at 12. He found that the sequence TGMEVGYW [which] has 6 of 8 amino acids in a consecutive peptide in both MOG and the vaccine is sufficient to cause clinically relevant neuroinflammation. *Id.* at 14. Based on the three *Gautam* articles, Dr. Steinman opined that the stretch of those sequence homologies was sufficient to trigger clinically relevant inflammation. The first *Gautam* paper from 1992 demonstrated that the injection of five of twelve, sometimes nonconsecutive amino acids of myelin basic protein (MBP), are sufficient to trigger EAE in mice. Pet. Ex. 77. A second article by *Gautam* demonstrated that a peptide with 4 of 11 MBP amino acids was able to stimulate CD4 T cells and induce neuroinflammation in mice. Pet. Ex. 78. Dr. Steinman then referenced a third study by *Gautam* et al, published six years later, that showed that 5 of 11 amino acids were identical between a herpes virus and MBP, with only 3 consecutive proteins and were capable of inducing EAE in some of the mice. Pet. Ex. 79. The authors of this paper noted that *Wucherpfennig and Strominger* have provided strong evidence that peptides derived from certain viruses and bacteria could stimulate MBP-specific T cell clones generated from MS patients. *Gautam* used a similar database search based on MHC and TCR contact residues and identified a herpesvirus (*Saimiri-HVS)* peptide with homology to the disease causing MBP 1-11 peptide. The *Gautam* group demonstrated for the first time that the HVS peptide stimulates the MBP 1-11 T cell hybridomas and induces clear clinical signs of EAE in some mice. *Id.* The paper recognized that the viral peptide did not stimulate EAE as strongly as the wild type MBP 1-11 but that it did stimulate all four T cell hybridomas in their

experiment. *Id.* at 8. The authors concluded, "these results indicate that a cross-reactive viral peptide can stimulate self-reactive T cells." *Id.*

Initially, Dr. Forsthuber argued that the *Gautam* studies required that specific amino acids needed to be in positions 3 and 6 in order to cause cross reactivity. Subsequently, he clarified that the positions are not so critical, but it is what is in the positions that is. Tr. 473. He then testified that different T cells have different preferences for binding and that you cannot predict what peptides will bind with the MHC molecule and which will stimulate an autoimmune response. *Id.* at 475, 479. He cast doubt on the likelihood of molecular mimicry because of the array of overlapping nine peptide sequences in the human body and in bacteria or viruses. Dr. Forsthuber contended, that the "activation of T cells by specific peptides is highly complex and exquisitely sensitive to a delicate balancing act of binding of a peptide to and properly aligning its sequence within the peptide-binding register of an MHC molecule." Resp. Ex. E at 6. He emphasized that typically autoimmune T cells are eliminated making it more complicated than randomly matching peptides. Tr. 475. However, it would appear that, in the case of the petitioner, his autoimmune T cells were not eliminated by thymic selection as they appear to be implicated in a rapidly developing, severe case of tumefactive MS that looked quite similar to the presentation of ADEM at the outset.

Dr. Forsthuber testified that Dr. Steinman does not know "definitively" exactly which of the six of eight amino acids would be needed to be in epitopes which would be needed to induce a reaction. He testified that "you can't *predict* just by looking at the sequence…it's impossible to predict what would bind…the chances that you're getting a wrong amino acid in the right position are much higher than getting by chance the right amino acid in the right position." Tr. 474. All in all he testified that because of the multiple factors involved, it was not possible to definitively predict what peptides would give rise to molecular mimicry and cause disease because of the complexity of factors he described.

During the course of Dr. Forsthuber's testimony, I indicated that I understood that it was very difficult to do the experiments that would lead scientists to be able to understand and predict the causes of human autoimmune disease such as MS, and that I understood the need to definitively control the number and placement of the amino acids in laboratory experiments in order to get reliable results in mice and that the odds of getting the wrong amino acids in the right place may be high. But I asked Dr. Forsthuber whether, in the real world, part of the explanation for rare events stimulated by the immune system is because sometimes these things (the proper alignments) do occur? Most of the time they don't but sometimes they do? He answered that that was a good question and that the answer is nobody knows. He felt that the concept of molecular mimicry based on sequence similarities is too simplistic and that it is more complicated than that. Tr. 476.

Regarding Dr. Steinman's testimony about sequences of similar amino acids, I find that he was providing an example of homology between amino acid sequences in the vaccine and MOG to illustrate homology as a way to explain the science using readily available resources. Dr. Steinman explained that he could not perform research on the petitioner, and most likely will never be able to do research on human subjects in cases in this court. He explained that such testing would be expensive, would require institutional review board consent, and would involve

obtaining of blood or CSF samples from before and shortly after onset which is generally impossible in the context of a vaccine case. Pet. Ex. 85 at 3. Dr. Forsthuber agreed that this was a very valid point that Dr. Steinman made. While it would be ideal to look at each molecular response to a vaccine in an individual petitioner, it is just not possible to test everybody and what their response against vaccine antigens would be. He agreed that ideally, we could test it, but it is a very involved process. Tr. 494. To be sure the critical time period for testing both before and after the onset of symptoms would have long passed by the time a case would be filed in the program.

Molecular mimicry has been an accepted theory in this Court and Dr. Steinman's BLAST search process has been accepted in a variety of cases involving demyelinating diseases, such as GBS, MS, TM, and ADEM. While prior decisions of special masters are not binding on my analysis, it is persuasive that molecular mimicry has been accepted in the program as a biological mechanism involving demyelinating conditions in multiple cases. *See, e.g.*, *See Davis v. Sec'y of Health & Human Servs.*, No. 14-978V, 2022 WL 1654743 (Fed. Cl. Apr. 27, 2022); *Maloney v. Sec'y of Health & Human Servs.*, No. 19-1713V, 2022 WL 1074087 (Fed. Cl. Mar. 17, 2022); *Pierson v. Maloney v. Sec'y of Health & Human Servs.*, No. 17-1136V, 2022 WL 322836 (Fed. Cl. Jan. 19, 2022*)*; *Koller v. Sec'y of Health & Human Servs.*, No. 16-439V, 2021 WL 5027947 (Fed. Cl. Oct. 8, 2021); *E.M. v. Sec'y of Health & Human Servs.*, No. 14-753V, 2021 WL 3477837 (Fed. Cl. July 9, 2021); *White v. Sec'y of Health & Human Servs.*, No. 15-1521V, 2019 WL 7563239 (Fed. Cl. Dec. 19, 2019); *Pasco v. Sec'y of Health & Human Servs.*, No. 16-500V, 2022 WL 6616736, at *27 (Fed. Cl. Sept. 23, 2022).

Dr. Steinman served as an expert in the *Quackenbush-Baker* case, in which I found the theory of molecular mimicry sufficient to explain how the vaccine could cause an aggravation of an asymptomatic or radiologically isolated MS. *Quackenbush-Baker v. Sec'y of Health & Human Servs.*, No. 14-1000V, 2018 WL 1704523, at *16 (Fed. Cl. Mar. 14, 2018). I found that petitioner's receipt of the flu vaccines in 2009 and 2011 made it more likely than not that she had a recall response when she received the 2013 flu vaccine, which contained several of the same components. *Id*. In that case there was also a rapid onset of MS symptoms. While my prior decisions or those of other special masters are not binding on my analysis, it is persuasive that Dr. Steinman's theories have been accepted as reputable, medical, or scientific mechanisms in other cases in this court and, in particular, in a case with similar facts to the present one.

The medical literature filed by petitioner establishes that molecular mimicry is a well-known theory in immunology that has been postulated numerous times in medical literature as a likely mechanistic theory to explain how infectious agents and vaccines can cause autoimmune disorders like ADEM, TM, MS, and GBS. Pet. Ex. 66. *Fujinami* and *Whitton* described molecular mimicry as one of three mechanisms that can initiate immunoreactivity leading to autoimmune disease. Pet. Ex. 75. To be sure, there are skeptics about the theory as evidenced by the *Trost* article among others. The quest for definitive proof has been successful only in a limited number of infections and autoimmune diseases. Nevertheless, molecular mimicry remains a primary theory of autoimmunity and Dr. Steinman has presented evidence as to how molecular mimicry triggered by the flu vaccine could have accelerated and aggravated the petitioner's MS condition. While I respect the detailed testimony presented by Dr. Forsthuber, I think the standard for proof that he proposes for analysis of a vaccine case is far higher than the

law requires. Congress created the Vaccine Program to recognize that adverse events do occur as a result of vaccinations. As stated in *Althen*, The Vaccine Injury Program is designed "to allow the finding of causation in a field bereft of complete and direct proof of how vaccines affect the human body." 418 F.3d at 1280. Both Dr. Steinman and Dr. Forsthuber concede that the science around molecular mimicry is growing, and definitive conclusions have not yet been reached in the scientific community. The case law in this program has held that, given the state of current scientific knowledge, petitioner need not make a specific type of evidentiary showing or require identification of a specific homology to prove that molecular mimicry is a sound and reliable theory by a preponderance of the evidence. Requiring proof of specific homology or proof of identical protein sequences giving rise to disease between the flu vaccine and the central nervous system in order to prove causation would require scientific certainty, which is a bar too high. *See Knudsen*, 35 F.3d at 549 (explaining that "to require identification and proof of specific biological mechanisms would be inconsistent with the purpose and nature of the vaccine compensation program").

The task of this court is not to *predict* what peptides may give rise to disease through molecular mimicry in a consistent and foreseeable manner, but rather to analyze whether there is sufficient evidence to indicate that it could have in this case. I find that Dr. Steinman's presentation was sufficient to demonstrate by a preponderance of the evidence that the flu vaccine received by Mr. Gardner on December 1, 2014 could have and was likely to have been the cause of the significant aggravation and acceleration of his MS condition. While I recognize that the theory has not been definitively proven, the testimony supports the concept that rare events, such as the one that occurred in this case, can be caused by molecular mimicry. This conclusion was well supported by the testimony of his treating MS specialist, Dr. Foley, who provided a detailed explanation of the correlation between the progressive onset of symptoms between December 3, 2014 and December 12, 2014, with the rapid development of a longitudinally extensive lesion in the cervical and thoracic spine in conjunction with the tumefactive lesion in the brain. Dr. Foley, early in the course of treatment, felt that the vaccine was causal in the progression of this disease and indicated that in the course of his extensive clinical experience treating MS patients that he has come to recognize that onset or aggravation of the disease is at times caused by vaccines.

For the reasons above, I find that petitioner has demonstrated a sound and reliable medical theory by preponderant evidence of how the flu vaccine he received on December 1, 2014 could have caused the significant aggravation of pre-existing MS. All of the doctors advocate vaccination for their MS patients and advocate for vaccination in general, but Dr. Steinman has demonstrated a theory that is sufficient to explain how the flu vaccine can cause an aggravation of a mild case of MS, and I have concluded that his theory has satisfied *Althen* Prong One.

**5. *Loving* Prong Five (*Althen* Prong Two): Petitioner has established a logical sequence of cause and effect between the flu vaccine and the significant aggravation of MS in his case.**

Above, under *Loving* Prong Three, I concluded that petitioner suffered a significant aggravation of his prior condition. Under *Loving* Prong Four (*Althen* Prong One), I concluded

that the influenza vaccine could cause an aggravation of a previously mild MS through the mechanisms of molecular mimicry and recall response. *Loving* Prong Five requires a petitioner to show a "logical sequence of cause and effect, showing that the vaccination was the reason for the significant aggravation." *Loving*, 86 Fed. Cl. at 144; see also *Althen*, 418 F.3d at 1278. This prong is sometimes referred to as the "did it cause" test; i.e., in this particular case, did the vaccine logically but not definitely cause the alleged injury. *Loving* 86 Fed. Cl. at 144.; *Broekelschen*, 618 F.3d at 1345 ("Because causation is relative to the injury, a petitioner must provide a reputable medical or scientific explanation that pertains specifically to the petitioner's case"). Temporal association alone is not evidence of causation. *See Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1148 (Fed. Cir. 1992).

This sequence of cause and effect is usually supported by facts derived from petitioner's medical records. *Althen,* 418 F.3d at 1278; *Andreu*, 569 F.3d at 1375-77; *Capizzano*, 440 F.3d at 1326; *Grant*, 956 F.2d at 1148. In this case it was also significantly supported by the opinion and testimony of his primary treating MS specialist. The Federal Circuit has held, "A special master should consider the causation opinions of treating providers, as "treating physicians are likely to be in the best position to determine whether 'a logical sequence of cause and effect shows that the vaccination was the reason for the injury." *Capizzano*, 440 F.3d at 1280.

**A. Petitioners' Experts' Opinions Regarding *Loving* Prong Five (*Althen* Prong Two)**

Dr. Steinman opined that the flu vaccine more likely than not significantly aggravated petitioner's MS. After demonstrating his theory of molecular mimicry, Dr. Steinman testified that petitioner's significant aggravation occurring rapidly and progressively was likely due to a recall response to the influenza vaccine that he received in December 2014 which had an identical H1N1 component as was contained in the 2010 vaccine which petitioner also received. Pet. Ex. 4 at 3; Pet. Ex. 16; Tr. 252-53. He testified that the theory of molecular mimicry with a recall response fit in petitioner's case because "recall immunity is very fast…sometimes it's hard to measure…sometimes the very fast response is not necessarily in a neutralizing antibody [but]…in a memory killer T cell." *Id.* at 252.

The history of the time period from December 1, 2014 forward is detailed above and is summarized here. There is no question that petitioner had an episode of optic neuritis in June of 2014, which appeared to have mostly resolved over the next couple months. In June, he had an MRI of the brain which demonstrated no evidence of demyelination in the brain but did show enhancement solely at the globe of the optic nerve. Pet. Ex. 3 at 8-9. He had no medical encounters between a follow-up at the Moran Eye Center in August and the December 1, 2014 appointment with Dr. Richards. There was no evidence of prior viral or bacterial infections during the months prior to December 1.

Mrs. Gardner testified that her employer was offering incentives for employees to do a full physical exam with their doctors at that time. She said that she had petitioner make an appointment and she did for herself as well because of this program. Tr. 10. Thus the appointment was made not because of any particular troublesome symptom, but simply for an annual physical. At that appointment on December 1, Mr. Gardner told Dr. Richards that in the last week he had experienced a sensation almost like pins and needles, mostly in his left foot but

extending up on the left to his abdomen which comes and goes and at times there is a heat sensation on the left thigh. Pet. Ex. 4 at 6. He received the flu vaccine at that appointment. A couple days later, he began to experience flu like symptoms. He continued to work until December 7, when he called in sick as he was feeling cold and achy and was barely able to use his right leg. Dr. Richards had apparently ordered blood work. Mr. Gardner came in on December 8, for the bloodwork, and the medical assistant noticed he was having difficulty walking at that appointment. She set him up to see Dr. Richards again. He saw Dr. Richards on Wednesday, December 10, when he told the doctor that his right leg felt worse since this past Monday (December 8). The note indicated that while standing there he could hardly lift his right leg up, his memory had not been as good as before and his brain was feeling foggy. Pet. Ex 4 at 9. He said the tingling in his left side was still present and he had a limp. He told Dr. Richards that two or three days after his last appointment his right leg went numb from his foot to his thigh. Dr. Richards suggested that he see a neurologist, but he did not decide to hospitalize him or make urgent arrangements to see a neurologist. Mr. Gardner went home.

When the Gardners awoke on December 12, Mrs. Gardner testified that her husband could not get out of bed. She had responsibilities at work, so she pushed him out of bed onto the floor. She went to work but returned an hour and a half later and found that he was still on the floor in the bathroom, and he could not urinate. She had to pull him down the stairs and put him in the car. She drove him to the Intermountain Medical Center emergency room. Tr. 18. He was admitted to the hospital through the ER. Upon admission, the initial MRIs were done demonstrating the tumefactive lesion in the brain and the extensive lesion in the spinal cord.

Dr. Foley explained that petitioner had only some pins and needles sensation on December 1, 2014. Within several days he was having some type of what appeared to be a systemic reaction to the flu vaccine. After a few days, he started to notice more neurological symptoms and then later in the time period he starts to get much worse to the point where his wife has to put him in the car to drive him to the hospital on December 12. At that point he had right leg paralysis, severe weakness and bladder dysfunction. Tr. 124.

Dr. Foley testified that an acute inflammatory lesion in the spinal cord that is gadolinium enhancing is going to manifest very, very rapidly as clinical symptoms. He correlated at least the onset of the cervical spine lesion with the rapid development of symptoms over the course of 12 days. He said that this rapid development of symptoms combined with the MRI demonstration of an enhancing tumefactive lesion in the brain and an extensive enhancing lesion in the cervical-thoracic spine suggests an open blood-brain barrier and blood-cord barrier. As such he thought that there was likely an open blood-brain barrier that exposed the CNS to the antigenic stimulus generated by the vaccine. He testified that the tight binding correlate of expanding inflammation in a very small space, in a very critical space, in the spinal cord will induce inability to walk and complete failure of bowel, bladder and sexual function very rapidly. He testified that the space in which the cervical-thoracic cord passes is less than the size of a half dollar. He said his theory would be that the bulk of that lesion burden, gadolinium enhancement, and cord enlargement developed within the first few days after getting the influenza vaccine. Tr. 143.

While petitioner had not had an MRI in the months immediately before December, he did have one in June which showed no evidence of MS lesions in the brain. He had at most mild

symptoms on December 1, which rapidly became worse beginning a few days later. Dr. Sriram agreed that these lesions were massively enhanced on December 12, but he said it was his best guess that they probably began to develop in October or November. Tr. 342.

Dr. Foley testified, as petitioner's treating physician, that petitioner's current diagnosis is "atypical MS." Tr. 105. He explained in his second expert report that petitioner's "MS was significantly exacerbated by the influenza vaccination, leaving him with permanent, severe disability following the vaccination." Pet. Ex. 63 at 1. Dr. Steinman agreed that petitioner had "an atypical case that had a lot of features of ADEM – that there was intense inflammation that caused horrible damage." Tr. 279. Both experts agreed that, within a few days of the flu vaccination, petitioner experienced flu-like symptoms, and after that began to experience more neurological symptoms as he complained of cognitive difficulties, vision changes, and persistent left leg numbness with the most prominent symptom becoming right leg dysfunction leading to paralysis by December 12, when his signs and symptoms had become severe. Dr. Foley classified this progression as an "acute event." He said petitioner's course "did not have the typical hallmark of a tumefactive MS event in that it developed so dramatically, had no oligoclonal bands in the CSF and was essentially monophasic which is why he initially called it ADEM. Tr. 106. The lack of oligoclonal bands is much more common in ADEM than in an acute tumefactive MS situation." *Id*. Dr. Foley also noted that he "elected to call it ADEM at the time," of diagnosis, "knowing that [he] was going to follow [petitioner] over time and that we would treat him as if he had ADEM." *Id*. Both Dr. Foley and Dr. Steinman indicated that there were no other identifiable causes of petitioner's significant aggravation. Tr. 144, 212. On cross examination, Dr. Foley stated that petitioner "met the McDonald criteria certainly on the basis of the optic neuritis and the acute ADEM-like event." *Id.* at 151. He said, it was not clear if petitioner would have met the criteria solely on the basis of the pins and needles at the beginning of the month, as this would not "count…as a bona fide event." *Id.*

Dr. Foley also testified that while mild cognitive complaints were expressed such as word finding difficulty, Mrs. Gardner testified that early in the time period she did not recall any cognitive issues and basically that his left leg was tingly. She thought that petitioner's symptoms at the time might have been stress related. Tr. 10. Dr. Foley explained that, consistent with the tumefactive lesion in the brain, the cognitive symptoms appeared to manifest more distinctly later in the course once petitioner was in rehab, which he thought was also consistent with his theory. Tr. 125.

Dr. Foley was asked how he interpreted the MRIs and correlated them with the symptom development. He said that when Mr. Gardner lost function in his legs by December 12, the doctors ordered MRIs of the brain and of the cervical and thoracic spine. Both the brain and spinal films were massively contrast enhancing. So, the process radiographically suggested a "major inflammatory storm kind of situation which clearly played out clinically." Tr. 108. Petitioner was then treated with high dose steroids which brought his legs back some. *Id.* at 107. They did a second MRI on December 22, which demonstrated slightly decreased edema and enhancement in the brain. The radiologist noted that the findings would be consistent with tumefactive MS with treatment response. Mild enhancement of the intraorbital optic nerve was seen, similar to the prior scan. An asymmetric atrophy of the right intraorbital optic nerve was also identified. On the spinal cord they noted an enhancing intramedullary lesion now extending

from C6 to T2 that measured 4.3 by .9 by .9 centimeters which was significantly increased from 2.8 by .8 by .6 on the prior scan. Dr. Foley indicated that we were seeing some improvement in the brain MRI as a result of the initial steroid treatment but some worsening in the spinal cord lesion burden during this time frame. Tr. 110-11. He testified that this was consistent with petitioner's legs becoming worse in the hospital. He was essentially paralyzed in the legs and the doctors then went to plasmapheresis. He said that this imaging presentation was significantly worse than a standard presentation of multiple sclerosis. With the background of no lesions in the brain in the June MRI, and the significant development of enhancing lesions corresponding with the rapid onset of symptoms in December, he characterized these lesions as more acutely reactive. Tr. 111-12.

A third set of MRIs was done on January 26, 2015 which showed a large left temporal lobe area of white matter T2 signal hyperintensity, with resolution of the previously seen associated edema and mass effect. There was slight volume loss on this scan which Dr. Foley explained would relate to neuronal cell death caused by the initial lesion burden. On the spinal cord films a mild fusiform cord lesion from C6 to T2 with mild residual post-contrast enhancement was seen, but no cord expansion, which had previously been seen on the prior two scans. The lesion was similar in extent but without the previous mass effect and demonstrated mostly resolved contrast enhancement. Tr. 113

Dr. Foley said that gradual resolution that was seen and this kind of symptom course "would be more typical of a real severe ADEM which is why [he is] calling it…an atypical MS." Tr. 115. The lesions have remained relatively stable with a little bit of variability with resolution of the swelling which allowed his spinal cord to take effect again and allow him to walk. He still has multiple problems but at least he can walk. *Id*.

He was asked if the lesions in ADEM and tumefactive MS can look the same and Dr. Foley said that they can. He said this was a rare and "real severe form of MS," described as tumefactive MS, which can have "significant amounts of edema with significant open blood-brain or blood-cord barrier dysfunction." Tr. 116. Thus, the first thing that comes to mind on this presentation is ADEM with these images, the clinical course and the monophasic large attack. *Id.* Dr. Foley further testified that petitioner obviously had optic neuritis before, but that this event is what left petitioner disabled. *Id.*

When asked to explain physiologically what was going on in the central nervous system, Dr. Foley said that there is an opening in the blood brain and blood cord barrier that occurs due to an antigenic stimulus and then circulating immune cells will rush in and if they aggregate will start to do several things. One is that they can swell the spinal cord and put pressure on the corticospinal tract going to the legs and it can compromise bowel and bladder function. These inflammatory aggregates can also start exerting a negative effect on the neuronal pools around them and start killing cells, killing neurons which ultimately led to the atrophy that we see in his scans years later. Tr. 121-22.

Dr. Foley was asked about the time course of what occurred in petitioner. He said that because we don't have an MRI immediately before the vaccination, we cannot say for sure. However, if you take from the time of the injection when petitioner had some mild

paresthesias—shortly thereafter he has some sort of reactive symptoms that suggest some systemic reaction to the flu shot. Then, after a few days, petitioner really starts to notice more and more neurological symptoms. Tr. 124. Dr. Foley explained that the spinal cord, especially the anterior cord where corticospinal tracts are very small – less than a half dollar around – lesion formation there is rapidly transmitted into clinical symptoms. *Id.* So, at the beginning we have only pins and needles paresthesias prior to the injection, and then after a couple of days it seems like he has reacted negatively to the flu shot, but not necessarily worsened neurologically. Then after that he really starts with this whole progression described in the testimony by Mr. and Mrs. Gardner where it takes her an hour to get him into the car to go to the hospital on December 12. *Id.* Dr. Foley continued, stating that an inflammatory lesion in the spinal cord will manifest in symptoms very rapidly, so it was his view that sometime in the first week after having the flu shot petitioner developed at least a spinal cord lesion that was rapidly and severely symptomatic. *Id.*

When asked about the role of the tumefactive brain lesion in the development of this disease, Dr. Foley said the lesion was primarily in the temporal lobe into the frontal lobe which would induce speech dysfunction, cognitive dysfunction, processing slowing, probably emotional abnormalities. Tr. 125. As we heard Mrs. Gardner testify, petitioner could hardly speak by the end of his admission. He said that we saw more of the brain symptoms come out during the rehabilitation stay, which is what he would expect as the time course for the development of cognitive symptoms secondary to the tumefactive brain lesion. *Id.*

Regarding petitioner's previous bout with optic neuritis in June 2014, Dr. Steinman noted that there was no clinical or radiographic evidence of disease activity elsewhere in his nervous system. Pet. Ex. 66 at 20. Further, on cross examination, Dr. Foley stated that, "the eloquent tissue in the spinal cord and…the progression of his clinical construct during the hospitalizations would be entirely consistent with new and enlarging lesions in eloquent tissue that had very little reserve areas…there would be a tight correlation between onset of clinical symptoms and the new and enlarging lesions and edema related to those lesions, especially in the spinal cord." Tr. 163-64.

Dr. Foley testified that petitioner's clinical presentation and MRIs "suggest a very open blood-brain barrier or blood cord barrier, and so there's just a lot of inflammatory process, and generally in MS, there will be a lot of oligoclonal bands generated with that." Tr. 107. Petitioner received high dose intravenous steroids and was transferred to a rehabilitation unit and "became completely paraplegic with no use of either leg," and continued bowel and bladder problems. Tr. 120-21.

On questioning by the Court, Dr. Steinman endorsed the concept that if petitioner had some level of MS at the time of the vaccination it is likely that the blood brain barrier was open and "even if it weren't open, the immune cells, once they're activated, they can go across the blood brain barrier, and if they get across and they recognize, for instance, MOG, they could stick there and cause damage." Tr. 308. Dr. Foley noted that respondent had a nice article by *DeKeyser*,[32] which for the most part he agreed with, in which they say in the following six weeks

[32] Jaques De Keyser et al., *Effects of influenza vaccination and influenza illness on exacerbations in multiple sclerosis*, 159 J. Neurol. Sci. 51 (1998).3 [Resp. Ex. A-3].

after an influenza illness, there was roughly a 33% incidence of relapse and that relapse after influenza vaccination is much less common—only about 5%. Tr. 128; Resp. Ex. A-3. So, he said, 5% is less common but it still occurs and obviously becomes 100% if it happens to you. He said that, fortunately, we see relapse secondary to the antigenic stimulus of vaccination much less frequently than after infection, but his busy neuroimmunology clinic sees one approximately every couple of months. Tr. 128.

**B. Respondent's Experts' Opinions Regarding *Loving* Prong Five (*Althen* prong two)**

Dr. Forsthuber and Dr. Sriram opined that petitioner's MS was already symptomatic at the time of the vaccination on December 1, 2014. Resp. Ex. A; Resp. Ex. B; Resp. Ex. F. Dr. Forsthuber wrote in his second expert report that "there is no reliable evidence that the influenza epitope claimed by Dr. Steinman as a 'molecular mimic' induces immunity, or that this sequence could generate and/or activate MOG reactive T cells," in petitioner. Resp. Ex. E at 21-22. Regarding the clinical picture, Dr. Forsthuber, although he acknowledged that he was not an MS clinician, agreed with Dr. Sriram that in "November 2014, Mr. Gardner noted left lower extremity weakness and paresthesias that were bilateral up to about T5,[33]" along with "cognitive changes, including word finding difficulties." Resp. Ex. E at 25; Pet. Ex. 17 at 1; Pet. Ex. 5 at 199. In his testimony, Dr. Sriram initially argued for the date of significant leg symptoms as December 1, because he asserted that the blood draw by the medical assistant who noticed his trouble walking took place on December 1. However, I have concluded that the most logical interpretation of the record is that the blood draw took place on the following Monday December 8, giving rise to the appointment on Wednesday, December 10. As noted above, the record referring to the blood draw said "*this* last Monday. Pet. Ex. 4 at 9 (emphasis added); Tr. 349. On December 1, he had a full physical by Dr. Richards, who recorded the pins and needles sensations that come and go on the left side. At this appointment, petitioner's eyes looked normal, extraocular movements were normal, and his range of motion was good in the hips, knees, ankles, back, shoulders and elbows. Pet. Ex. 4 at 7. There was no complaint of weakness. While he reported on December 10, that his right leg had stopped working several days before, the petitioner was still able to walk on his own, both on December 8 and 10. There was no complaint of cognitive issues on December 1. It was not until the morning of December 12, that he became paralyzed and unable to urinate. His wife had to drag him down the stairs and get him into the car to go to the hospital on that day.

Dr. Sriram stated in his first expert report that petitioner's "symptoms preceded the receipt of the influenza vaccine on December 1, 2014," and the "neurological processes of myelitis was already underway at the time he received his vaccine." Resp. Ex. B at 6-7. When asked if the petitioner had active lesions in his brain prior to vaccination, Dr. Sriram stated "I would suspect so." Tr. 340. Further he stated that petitioner,

> had fairly large lesions that were enhancing on December 12, [2014] and these include his brain and spinal cord…many of his lesions, especially his cognitive, came because of his lesion in his left side of the brain that involved the frontal lobe and the temporal lobe. The clinical picture that he has, especially word-finding

[33] There was no reference to "bilateral" sensory changes on December 1, only left sided paresthesias.

> difficulty, is very typical of nondominant hemisphere lesions in individuals who are right-handed.

Tr. 340-41.

Further, Dr. Sriram testified that "it's unlikely that these enhancing lesions especially as large as they are and they're called tumefactive, they last for a long time…if those lesions began to disappear as they did in the January 22, 2015 MRI, then they must have started way, way back, because large lesions take more than three to four months to be active." Tr. 340-41. Dr. Sriram's "best guess," was "if these lesions were massively enhanced on December 12 and they weaned off by January 22, these large lesions…last longer than three to four months, so it's up a timeline for the beginning of this sometime in October, November… because these large lesions don't suddenly come up and suddenly disappear." *Id.* at 342.

Over objection of counsel because it was not submitted in evidence in this case, Dr. Sriram cited to the well-known *Cotton* paper,[34] with which the court was quite familiar. He suggested that the *Cotton* study supported his view that lesions that were significantly enhancing by December 12, were likely enhancing for three to four months. Tr. 342. However, I observed that *Cotton* documented that gadolinium enhancement was evidence of an acute and active inflammation and that you are talking about a week or two for gadolinium enhancement and that the enhancement can disappear in a matter of weeks as well. *Id.* at 343. Dr. Sriram did not disagree with my characterization of *Cotton,* and after review of the article as referenced in the footnote, I find that study to be quite supportive of Dr. Foley's description of the progression of the lesion in this case. *Cotton* observed that they were able to detect some large, ring-enhancing lesions within 1 to 6 days and that most lesions enhanced for one to two weeks while some persisted for more than four weeks. There was no finding that large lesions must be enhancing for three to four months. Assuming that the lesions had developed in the first week of December, the January 26, MRIs did not show that the lesions had disappeared, but only that the edema was gone and the enhancement was reduced.

On cross-examination, Dr. Sriram testified that medical records alluding to memory issues prior to the vaccination would *not* classify as a McDonald event "because we don't have sufficient data for that." Tr. 398. Later in the cross-examination, Dr. Sriram testified that petitioner demonstrated "two separate events, separated in time and space," the first was the optic neuritis and the second was on "December 1, [2014] when he presented to the family doctor for a vaccine shot and complained of sensory abnormalities in his feet and his legs." Tr. 409. Further, Dr. Sriram opined that it is not mandatory to have a neurological examination to make a diagnosis on McDonald criteria, "we can construct from the history and from the

[34] Cotton et al., *MRI contrast uptake in new lesions in relapsing remitting MS followed at weekly intervals*, *Neurology*, 60 Neurol. 640 (2003). In this landmark study 26 patients with relapsing-remitting MS were imaged with MRI weekly for eight weeks and every other week for 16 weeks. Previous studies had not imaged more frequently than monthly. The authors wrote, "The salient finding of our study is that the majority of new lesions in RRMS demonstrate enhancement for only 1 or 2 weeks." *Id.* at 643. The authors did indicate that larger, ring enhancing lesions do tend to enhance longer, but noted that they observed enhancement within 1 to 6 days after the beginning of BBB breakdown in some patients with larger lesions. *Id.* at 645. They concluded, "In a given patient, some new lesions could be nodular while others were ring-shaped, and enhancement could persist less than 2 weeks in some of the new lesions while some other new lesions would enhance more than 4 weeks. *Id.*

expression of the symptoms that the patient gives that this is most likely a second event." Tr. 410. He stated that "this event lasted for a couple of days, had a clear anatomical distribution involving the left leg, going up to the abdomen, fit an anatomical representation of the spinal cord, and so that would be a sensory event." *Id*.

While in retrospect it appears likely that the sensory symptoms in the left leg did indicate a mild presentation of relapsing-remitting MS as Dr. Foley agreed, Dr. Sriram appeared to place too much emphasis on purported cognitive issues prior to vaccination which largely involved some complaints of word finding problems and were sufficiently mild that his wife never noticed them. *See* Tr. 340. The cognitive issues did not actually become prominent until well into petitioner's hospitalization and indeed did become severe during that time, consistent with the manner in which Dr. Foley explained would be likely to occur secondary to the tumefactive brain lesion developing in December. On questioning by the Court, Dr. Sriram agreed with Dr. Foley that the most long lasting and significant symptoms for petitioner related to lesions in the C6 to T2 spinal cord, rather than the brain lesions. These deficits including bowel and bladder issues, are attributable to the spinal cord lesions and have not completely improved. *Id*. at 358. The Court asked Dr. Sriram about the significant inflammation in the spinal cord correlating with the dramatic changes in symptoms that occurred around December 12, 2014. Dr. Sriram responded, "I cannot say whether he had no inflammation at all prior [to the vaccination], because he had symptoms prior to that." Tr. 363. Dr. Sriram agreed that petitioner experienced dramatic changes in his symptoms and that "often happens in spinal cord lesions…[because] the spinal cord is a very small area, and you have inflammation, and you can get massive involvement of many of the tracts going up and down." Tr. 363.

Dr. Sriram opined in his expert report and at the hearing that "the vaccine did not change what had otherwise been in this case a fairly tragic course of events." Tr. 379. He agreed with Dr. Foley that petitioner's presentation on December 12, 2014 was atypical because he developed tumefactive lesions, and "you don't see tumefactive lesions in the garden variety MS." *Id.* at 409. Dr. Sriram ultimately opined that when petitioner received the flu vaccination on December 1, 2014, "he had a classic clinical description of myelopathic features of a sensory involvement from his left foot up to his abdomen, affecting one limb, and this was consistent with an anatomical representation of the spinal cord. *Id.* at 411. Given the prior history of optic neuritis he considered that these symptoms represented a second, separate in time event and thus a diagnosis of MS could be made at that time. *Id.*

Dr. Forsthuber testified that after vaccination the immune response is slow. He said that the antigen first goes to the lymph nodes, which takes three days. Tr. 519. Further he testified that "whether the blood-brain barrier is open or not [the]…influenza vaccine is an antigen that's deposited in the arm…it's not going to the brain." *Id*. On direct he agreed that regardless of the state of inflammation in petitioner's brain at the time of the vaccination, it does not change the T cell process and the antibody production process – that would take more than one to three days to produce evidence of clinical disease. Tr. 523-24. Dr. Forsthuber concluded that it is immunologically impossible for petitioner's body to produce symptoms within one to three days of vaccination. *Id*.

### C. Discussion and Conclusion Regarding *Loving* Prong Five (*Althen* Prong Two)

The fifth *Loving* prong and second *Althen* prong requires proof of a logical sequence of cause and effect showing that the vaccine was the reason for the injury, usually supported by facts derived from a petitioner's medical records. *Althen*, 418 F.3d at 1278; A*ndreu*, 569 F.3d at 1375-77; *Capizzano.*, 440 F.3d at 1326; *Grant,* 956 F.2d at 1148. In determining whether petitioner has put forth preponderant evidence of *Althen* Prong Two, the undersigned generally takes into consideration the opinions of treating physicians. As recognized by the Federal Circuit, the opinions of treating physician are typically "favored" as treating physicians "are likely to be in the best position to determine whether a 'logical sequence of cause and effect show[s] that the vaccination was the reason for the injury.'" *Capizzano*, 440 F.3d at 1326 (quoting *Althen*, 418 F.3d at 1280). However, treating physician's views do not bind the special master, *per se*; rather, their views should be carefully considered and evaluated. § 13(b)(1); *Snyder v. Sec'y of Health & Hum. Servs.*, 88 Fed. Cl. 706, 746 n.67 (2009). "As with expert testimony offered to establish a theory of causation, the opinions or diagnoses of treating physicians are only as trustworthy as the reasonableness of their suppositions or bases." *Welch v. Sec'y of Health & Hum. Servs.*, No. 18-494V, 2019 WL 3494360, at *8 (Fed. Cl. Spec. Mstr. July 2, 2019).

In this case, the primary treating physician, Dr. Foley, is an experienced MS specialist and director of the Rocky Mountain MS Clinic which sees about 4,200 patients a year with MS, ADEM, transverse myelitis and optic neuritis. Dr. Foley analyzed the record with the benefit of his firsthand involvement in petitioner's care. He testified that we have to call this an atypical MS, that had a monophasic, severe episode that was ADEM-like. Tr. 118. He said that the sensory symptoms in the left leg reported on December 1, when viewed in conjunction with the optic neuritis event the prior summer that had been validated by a neuro-ophthalmologist could have been a prodrome. As noted above, however, petitioner had a complete physical on December 1, when there was no complaint of weakness, or cognitive issues and range of motion in all joints was normal. There was no inability to walk. Dr. Foley said that he then followed a typical ADEM like course with the rapid development of severe inflammation that gradually expanded and worsened over a week or two or three. Tr. 121. Noting that Mr. Gardner's symptoms, which became dramatically worse by December 12, included inability to walk with bowel and bladder dysfunction, continued to worsen over the course of his hospitalization when his lower extremities became completely paralyzed. He developed significant cognitive problems during the course of his hospitalization consistent with the more gradual impact of his brain lesion as described by Dr. Foley. Critical to his persuasive analysis was the explanation of the rapid progression of Mr. Gardner's neurological symptoms after his initial flu like symptoms which was caused by the large and massively enhancing lesion in the spinal cord.

I asked Dr. Foley if he could explain physiologically what was going on that caused the petitioner to rapidly develop paralysis, bowel and bladder dysfunction and the other problems he developed during December. Dr. Foley explained that the initial thought is there is an opening in the blood brain barrier and the blood cord barrier that usually occurs in response to a stimulus and then circulating immune cells will rush into certain areas that are usually perivenular and those cells if they aggregate in sufficient numbers will start to do a couple things. One is that

they can swell the spinal cord or the brain, so they get this swollen look with acute inflammation as occurred in this case. The swelling in the spinal cord can actually put pressure on things like the corticospinal tract which is your major motor tract going to the legs and it can compromise bowel and bladder function. At the same time the inflammatory aggregates also start exerting a negative effect on the neuronal pools which ultimately lead to atrophy that we see in the scans years later. Tr. 122. If proper intervention is not undertaken, you can very well remain paralyzed permanently. He said even with proper intervention, as we could see in petitioner's testimony, he is certainly not back to normal. *Id.*

Dr. Foley explained that the blood-brain and blood-cord barriers consists of a set of cells that encircle the blood vessels that get in the brain. The body does not allow random cells to enter central nervous system tissue. So, in general, there are tight junctions in the blood brain barrier that do not allow much trafficking at all and that in normal circumstances let very little through to the central nervous system. There is a little bit of immunological surveillance in brain parenchyma to look for viruses or tumors in a normal circumstance. But when the blood brain barrier is opened it is like tearing a rent in the barrier, probably in several different locations and when this happens you get florid diffusion of cells and of course the gadolinium enhancement on the MRI. The gadolinium flows right through the open barrier and acts as a surrogate for the immune cells rushing through which enables physicians to see where the demyelination and inflammation is occurring. Tr. 127.

In terms of the logical progression in this case, Dr. Foley said that we obviously do not know exactly what his scans would have looked like if one had been done shortly before December 1. But we do know that there was no indication of MS on the MRI done in June. Dr. Foley explained that at the time of injection we only have pins and needles paresthesias in the left leg. Then there is in a couple of days where it seems like he has sort of reacted negatively to the flu shot, but has not experienced, necessarily, worsened neurological symptoms. Then he really starts this whole story that he related in his testimony where it took his wife an hour to get him into the car on December 12, when he had severe weakness and bladder dysfunction. Dr. Foley explained an acute inflammatory lesion in the spinal cord that is gadolinium enhancing is going to manifest very, very rapidly as clinical symptoms. He testified, that in his opinion, sometime in the first week after having the flu shot, he developed at least a spinal cord lesion that became nearly immediately symptomatic. Tr. 124-25. He explained that the role of the tumefactive lesion in the brain that would induce speech dysfunction, cognitive dysfunction, processing, and slowing, and probably emotional abnormality was more gradual. As Mrs. Gardner noted, her husband could hardly talk by the end of his hospital admission. Dr. Foley said the cerebral lesions, particularly when they occur in the white matter as they have here, can take longer to manifest with clinical symptoms than those in the cervical and thoracic spinal cord. *Id.* Dr. Sriram agreed that the major symptoms of paralysis and bowel and bladder symptoms were caused by the spinal cord lesion and can occur rapidly. Tr. 363.

Dr. Foley said that the antigenic stimulus that leads to this aggravation can come from the live flu virus or the vaccine. He said they see relapses of MS after both the wild infection and vaccination. Fortunately, it is much less frequent after vaccination but as noted in the *DeKeyser* article relapse occurs about 5% of the time after vaccination and he estimated that they see post vaccinal relapse in a busy MS clinic once every month or two. Tr. 128.

Dr. Foley stressed that the presentation of this sentinel event, and its progression would have been called frank ADEM but for the prior optic neuritis. Therefore, he is calling it an ADEM- like atypical MS. He said that petitioner may have gone on to a relatively mild course of MS but for the receipt of the flu vaccine at a time when the blood brain barrier was open as evidenced from the mild symptoms at the time of vaccination. I found sound and reliable Dr. Foley's detailed explanation of the tight binding correlate in the critical space in the cervical/thoracic spinal cord giving rapid rise to the inability to walk, complete failure of bowel and bladder, and sexual dysfunction in conjunction with the massive gadolinium enhancement on the MRIs. I also find persuasive his explanation of the likely role of the antigenic stimulus from the vaccine, received at a vulnerable time when the blood brain barrier was likely already open allowing for a rapid and massive stimulus. The strong and rapid response to the vaccine was also likely secondary to a recall response, Mr. Gardner having been exposed to the same antigen in a vaccination several years before.

While it is not possible to know definitively, to what extent Mr. Gardner had lesions prior to December 1, I find Dr. Foley's detailed explanation of the correlation between the development of the spinal lesion and the progressive onset of significant symptoms over 12 days to be much more persuasive than speculation based solely on the size of the lesion. Dr. Sriram's reference to the *Cotton* article provides support for the rapid development of enhancement on MRI and no support for the notion that the lesions would have had to have been present for three or four months before December 12. Indeed, because petitioner had the mild symptoms, it would appear logical and likely that the blood brain barrier was open at the time the vaccine was administered. The early flu like symptoms a couple days after the vaccination suggest the activation of the immune system in response to the vaccine. The combination of these factors facilitated the early and abundant access of the responding immune cells to the central nervous system leading to the dramatic worsening of symptoms and massive gadolinium enhancement on MRIs done twelve days post vaccination.

Importantly, had he not had the vaccination at this inopportune time, I find that it is more likely than not that petitioner could have gone on to a milder, garden variety MS event. However, because of the immune stimulus from the vaccine at a time when it is likely that the blood brain barrier was already open, he developed a more virulent course. Unfortunately, this led to the monophasic event with the severe symptoms that progressed through his hospitalization. The lesions stabilized but did not disappear as contended by Dr. Sriram. After the inflammation moderated, he did experience some significant reduction in symptom severity but the severe lesion burden from this sentinel event has left him with permanent damage and disability. Dr. Foley explained that the extendive lesion in his cervical and thoracic spinal cord, already is showing myelomalacia after several years and the cord is actually shrinking. Same is true in the left temporal and frontal lobe where he is demonstrating atrophy. I find that the detailed, sound and reliable explanation provided by Dr. Foley is persuasive that the immune response to the influenza vaccine more than likely massively accelerated both the severity and extent of petitioner's central nervous system compromise from which he will not fully recover. Tr. 130.

While the issue of molecular mimicry as explained by Dr. Steinman and disputed by Dr. Forsthuber presents a much closer call, I recognize that given the present state of medical knowledge, the demonstration of homology in an immunologically significant area such as MOG is sufficient to demonstrate a theory of how the vaccine *could cause* the harm in this case. Above, I concluded that petitioner provided a sound and reliable theory for how the flu could cause a significant aggravation of a mild MS. To demonstrate *Loving* prong five, petitioner must show that there is a "logical sequence of cause and effect showing that the vaccination was the reason for the injury." *Capizzano*, 440 F.3d at 1324. While I agree with Dr. Forsthuber that the theory has not been definitively proved in petitioner's case, the Vaccine Act does not require such definitive proof. Here, the medical records demonstrate that, prior to the vaccination, petitioner only had a mild case of MS, with very limited symptoms on his left side. Several days after the vaccination, petitioner developed extensive symptoms in his right leg and ultimately by December 12, paralysis in the right leg and loss of bowel and bladder function which appeared to correlate most closely with the development of a large and longitudinally extensive spinal cord lesion. Furthermore, petitioner's treating physician, Dr. Foley, provided an opinion that the flu vaccine significantly exacerbated petitioner's MS with which opinion Dr. Steinman agreed.

The sequence of cause and effect is usually supported by facts derived from petitioner's medical records. *Althen,* 418 F.3d at 1278; *Andreu*, 569 F.3d at 1375-77; *Capizzano*, 440 F.3d at 1326; *Grant*, 956 F.2d at 1148. In this case, it was also significantly supported by the opinion and testimony of his primary treating MS specialist. The Federal Circuit has held, "A special master should consider the causation opinions of treating providers, as "treating physicians are likely to be in the best position to determine whether 'a logical sequence of cause and effect shows that the vaccination was the reason for the injury." *Capizzano*, 440 F.3d at 1280.

Based on the opinions of Dr. Steinman and Dr. Foley I have concluded that the petitioner has provided preponderant proof of a logical cause and effect between the vaccine and his severely aggravated case of multiple sclerosis. As such, he has proved *Loving* prong five and *Althen* prong two.

### D. *Loving* Prong Six (*Althen* Prong Three): Petitioner has established a medically acceptable temporal relationship between the flu vaccine and the exacerbation of Mr. Gardner's MS.

The final *Loving* prong requires petitioner to establish a "proximate temporal relationship" between the significant aggravation of his condition and the received vaccine. *Loving* 86 Fed. Cl. at 144; *see also Althen*, 418 F.3d at 1281. That term has equated to the phrase, "medically-acceptable temporal relationship." *Althen* at 1281. A petitioner must offer "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation." *de Bazan v. Sec'y of Health & Human Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008). The explanation for what is a medically acceptable timeframe must also coincide with the theory of how the relevant vaccine can cause an injury (*Althen* prong one). *Id.* at 1352.

The explanation for what is a medically acceptable time frame must also coincide with the theory of how the relevant vaccine can cause the injury alleged (under *Althen* Prong One). *Id.*; *Koehn v. Sec'y of Health & Hum. Servs.*, 773 F.3d 1239, 1243 (Fed. Cir. 2014); *Shapiro*, 101 Fed. Cl. at 542; *see also Pafford*, 451 F.3d at 1358. A temporal relationship between a vaccine and an injury, standing alone, does not constitute preponderant evidence of vaccine causation. *See, e.g., Veryzer*, 100 Fed. Cl. at 356 (explaining that "a temporal relationship alone will not demonstrate the requisite causal link and that [P]etitioner must posit a medical theory causally connecting the vaccine and injury").

**1. Petitioner's Experts' Opinion Regarding *Loving* Prong Six (*Althen* Prong Three)**

Petitioner's experts agreed that petitioner initially experienced flu like symptoms within a few days or within one to two days post vaccination. Both noted that he had to call into work sick, which call-in took place on December 7. Petitioner stated in his affidavit that he called in sick to work on December 7, and told them he was "feeling extremely cold and achy and [he] was barely able to use [his] right leg." Pet. Aff. ¶ 5. As stated in respondent's Ex. A-2, 30-35% of flu vaccine recipients report systemic symptoms such as headache, myalgia, (muscle aches) malaise fatigue and fever which may correlate with an increase in inflammatory cytokines.[35] Within one or two more day after the onset of the flu like symptoms he began to experience more neurological symptoms. The report of his call-in to work suggests a combination of flu like symptoms and neurological symptoms by that time. His symptoms progressed such that the primary focus switched from mild pins and needles on the left side initially to numbness and then weakness in his right leg as noted by Dr. Richards on December 10. The symptoms continued to progress to the point of right leg paralysis and inability to urinate by December 12. Those symptoms continued to worsen in the first part of his hospitalization.

As explained above, Dr. Steinman attributed the relatively rapid onset of symptoms to a recall response, from petitioner's receipt of an influenza vaccination in 2010, which had the same H1N1 component that was present in the vaccine received on December 1, 2014. Tr. 252-53.

Both Dr. Steinman and Dr. Foley recognized that Mr. Gardner had the prior documented episode of optic neuritis in June 2014 with some improvement by his August appointment with Dr. Warner and that in histories given in the hospital he noted some tingling in his left leg which lasted for several months. At his December 1, appointment for a physical he told Dr. Richards that in the last week he felt something almost like pins and needles mostly in the left foot but at times going up to the abdomen on the left. As he described them at the time, these left leg tingling symptoms appeared to be a new presentation in the week or so before the vaccination.

Dr. Steinman stated that "recall immunity is very fast…sometimes it's hard to measure…sometimes the very fast response is not necessarily a neutralizing antibody [but]…in a memory T cell." Tr. 252. Citing to papers by *Serane*, *Fan*, and *Kardjito*, Dr. Steinman drew a comparison between the tuberculin test for tuberculosis, and petitioner's onset of symptoms via

[35] Lisa Christian et al., *Proinflammatory cytokine response correspond with subjective side effects after influenza virus vaccination*, 33 Vaccine 1360 (2015).

molecular mimicry and recall response. Tr. 251. He testified that if an individual "had been exposed to tuberculin or had tuberculosis, that arm might get red and angry in 24 hours or less." Tr. 251.

Citing to a paper by *Kappos*, Dr. Steinman testified that it is not known why the onset of a hypersensitivity reaction via molecular mimicry varied from patient to patient, and therefore why petitioner did not have a reaction to any earlier flu vaccines. Tr. 254-55. In that paper the authors tested the injection of altered peptide in multiple administrations. Most patients did not have a rapid recall response until after several doses but one did have a hypersensitivity response after the second. Dr. Steinman stated that "humans have a variety of different bad response to these molecular mimics." *Id*.

Dr. Foley testified that petitioner's MRIs on December 12, 2014, demonstrated massively enhancing lesions which suggest a very open blood brain barrier. Tr. 107. Further he stated that the lesions suggested that radiographically there was a "major inflammatory storm kind of situation, which clearly played out clinically." *Id.* at 108. Dr. Foley concluded that petitioner demonstrated an atypical case of tumefactive MS which had presented similarly to ADEM and that the dramatic change in symptoms over the 12 days after vaccination correlated with an inflammatory response in the small space of the cervical and thoracic spinal cord with expanding inflammation and edema in the cord. He opined that "the bulk of the lesion burden, gadolinium enhancement, and cord enlargement developed within the first few days after getting the influenza vaccine [which]…induce[d] inability to walk and complete failure of bowel, bladder, and sexual function very rapidly." *Id.* at 143. As detailed above, the changing and worsening neurological symptoms progressed to the point of right leg paralysis and bowel and bladder dysfunction over at least a 12-day period with further worsening after petitioner was hospitalized before the symptoms stabilized.

**2. Respondent's Experts Opinions' Regarding *Loving* Prong Six (*Althen* prong three)**

Respondent argues that petitioner failed to provide evidence of a medically acceptable timeframe between petitioner's receipt of the flu vaccination and the onset of his alleged multiple sclerosis symptoms. Resp. Post Hearing Brief at 46. Further, respondent argues that petitioner did not provide adequate evidence that he received the flu vaccine in 2010 that serves as the basis of Dr. Steinman's recall response theory, and that even if the recall response was medically reasonable, petitioner has not presented reliable evidence of a 1-3 day onset, and that a 1-3 day onset is not medically reasonable. *Id*. at 48-51.[36]

Dr. Forsthuber wrote in his first report that "molecular mimicry theory still remains one of the best supported and conceptually most logical theories for the induction of autoimmune disease…autoreactive T cells involved in the pathogenesis of MS immunologically recognize CNS autoantigens, such as MBP or MOG, presented by antigen presenting cells via their T cell receptor." Resp. Ex. A at 5. Dr. Forsthuber testified that the process of molecular mimicry producing an onset of worsening neuroinflammation is not possible within one to three days of the vaccination. Tr. 501. He further testified that following vaccination "predominantly

[36] The Court has concluded that there was adequate evidence that he did receive a flu shot in 2010.

antibodies," are produced in the body, and "there are obviously some T cells produced, because you need…to help antibody production." *Id*. He explained that there are two classes of T cells, the first are T helper cells which are CD4 positive and they recognize peptides presented by MHC class II molecules and cytotoxic CD8 T cells which recognize peptides presented by MHC class 1 molecules. Tr. 501-02. He explained that CD4 helper T cells help B cells to produce antibodies and have functions in producing cytokines. On the negative side, they also contribute to the pathology of autoimmune diseases. *Id.* Dr. Forsthuber defined a recall or memory response as "an immune response to the same antigen in an individual that has a preexisting immune response to this antigen, or…if an individual has encountered an antigen and then reencounters this antigen." Tr. 503. In contrast to a primary immune response, in a memory response "there are more numbers of T cells around." *Id*.

He testified that after a vaccination "an immune response doesn't just happen," there are defined sequence of steps. Tr. 504. The first step, happening from six to 24 hours, but "probably around 12 hours," after the vaccination. It will start by activating a local immune response in the local muscle cells in the deltoid, recruiting more inflammatory cells to the site in the arm. *Id*. at 504-05. Dr. Forsthuber said then more inflammatory cells are then recruited, primarily dendritic cells which "are the engineers of an immune response, because dendritic cells, are cells that take up the antigen and then transport the antigen to local draining lymph nodes." *Id.* at 505. The second step involves the dendritic cells carrying the influenza antigen to the local draining lymph node, which takes an additional 6 hours, approximately 24 hours after vaccination. *Id*. at 506. The third step involves the dendritic cells secreting cytokines, leading to "increased recruitment of T lymphocytes and B lymphocytes," which takes another 12 to 24 hours. *Id*. By the end of day three, the T cells circulate into the blood stream and help B cells make antibodies. *Id*. at 509-10. The T cells are "looking for the place where they can encounter their antigen again, which for MOG-reactive T cells is the central nervous system, the brain or the spinal cord." Tr. 510. Dr. Forsthuber's conservative estimate was that it takes T cells "two to three days at least for them to arrive in the brain." *Id*. In the next six to ten hours, the T cells "need to re-encounter the autoantigen that they're specific for in the brain. They become reactivated in the brain by antigen presenting cells in the brain, like local microglia or even dendritic cells." *Id.* at 511. The final step in six to 12 hours involves the creation of cytokines and the creation of damage." *Id*. at 511-12. Dr. Forsthuber estimated that this entire process post-vaccination would take anywhere from 4-5 days. *Id.* at 512.

From a clinical standpoint, Dr. Sriram testified that petitioner had "fairly large lesions that were enhancing on December 12, [2014] and these include his brain and the spinal cord." Tr. 340. He attributed petitioner's cognitive difficulties to the involvement of the enhancing lesions in his frontal lobe and temporal lobe. *Id.* at 340-41.

Disagreeing with Dr. Foley and Dr. Steinman, Dr. Sriram testified that he assumed that the lesions must have been around for three or four months because they were large and that they would not have begun to disappear by January 22, if they were new. He noted that his assumption was based on his thinking that the large lesion would take three to four months to be active. Tr. 341.

**3. Discussion and Conclusion Regarding *Loving* Prong Six (*Althen* Prong Three):**

In this case, both parties and their experts devoted significant attention to the timing of petitioner's symptoms and to whether an immune response could have caused the onset of a systemic response leading to a significant aggravation of petitioner's underlying MS in the timeframe involved in this case. When petitioner appeared in Dr. Richards's office for a general physical exam on December 1, he mentioned that for the past week he had experienced a sensation almost like pins and needles, mostly in his left foot but extending up the left leg to his abdomen which comes and goes. His physical exam, including range of motion in all joints was completely normal. Given the history of optic neuritis in June 2014, without any MS lesion burden on MRI at that time and the subsequent history, it appears that he was likely experiencing mild symptoms of MS at the time that he received the flu vaccine. This also suggests that there was likely an open blood-brain and/or blood-cord barrier at that time. *See* Tr. 123-26, 309-10.

A couple days later petitioner began to experience flu like symptoms—these were described as feeling achy and cold, but he continued to go to work until December 7, when he called in sick describing those symptoms, but also that he was barely able to use his right leg at that point. On December 8, he was scheduled to return for blood work following his physical and the medical assistant noticed that he was having difficulty walking and scheduled him to come back to see Dr. Richards again on December 10. At that appointment he described that his right leg rather than his left had gone "intensely numb." It did not hurt but felt like it had fallen asleep. Dr. Richards recorded that all muscle groups on the right lower extremity are significantly weaker than the left. He noted that he walks with difficulty but without assistance. The Babinski, an upper motor neuron sign, was positive on the right and neutral on the left. Pet. Ex. 4 at 9.

Two days later, petitioner was no longer able to walk without assistance and, as his wife described, she had to drag him down the steps and into the car to go to the hospital where she put him in a wheelchair to enter the emergency department. He was not able to urinate at this point and was admitted.

The MRIs, from December 12, as described above, demonstrated a large and peripherally enhancing lesion in the left anterior temporal lobe with edema, and a prominently enhancing, T2 hyperintense lesion at the C6 to T1 levels of the spinal cord. Pet. Ex. 5 at 14-21. He had a second set of MRIs done ten days later on December 22. The second brain scan showed significantly decreased edema associated with the lesion, but the enhancement had only minimally decreased in the brain. The spinal film continued to demonstrate an enhancing intramedullary lesion within the cervico-thoracic cord. In addition, there was increased T2 hyperintensity of the central gray matter pattern on the axial views. The spinal lesion now measured at least 4.3 cm cranial-caudal and now extended from C6 to T2. *Id.* at 319-25.

He was hospitalized at the Intermountain Medical Center and Intermountain Rehabilitation Hospital from December 12, 2014 through January 9, 2015. During that time, he was treated with steroids, plasmapheresis and physical and occupational therapy. His condition deteriorated to the extent that he was essentially paralyzed below the waist, was unable to speak

at times and developed increasing cognitive and visual problems. On discharge, he required stand by assistance for activities of daily living, and with performance of complex tasks. Pet. Ex. 5 at 631-33 His discharge diagnoses were MS, lower extremity paraplegia, T4 sensory level, optic neuritis cognitive deficits, urinary retention and constipation. *Id.* at 631.

On January 19, petitioner saw Dr. Foley as an outpatient. On physical exam his strength was 0/5 bilaterally in the lower extremities with multiple sensory and coordination deficits. Dr. Foley carefully reviewed the history of this illness and ordered a third set of MRIs which were done on January 26, approximately six weeks after his initial hospitalization. The brain scan showed extensive white matter T2 signal hyperintensity involving the anterior lateral left temporal lobe extending along the subependymal white matter. The T2 signal intensity was significantly diminished as was the degree of post contrast enhancement which was now present but minimal. There was an area of suggested white matter loss in the affected area. There continued to be a fusiform, inhomogeneous lesion with T2 hyperintensity running 8 cms from C6 to T2—now with slight enhancement. Pet. Ex. 6 at 5-12.

Dr. Steinman opined that petitioner likely had a recall response to the flu vaccine which had the identical H1N1 component to the one he had received in 2010. He further testified that "recall immunity is very fast…sometimes the very fast response is not necessarily in a neutralizing antibody. It's in a memory killer T cell." Tr. 252. Dr. Steinman described an article by *Lai et al.,* that showed that, during a recall response, reactive memory cells can react "within six hours [of the vaccine], ... not just days[.]"[37] Pet. Ex. 108. The study demonstrated that *naïve* CD4 T cells exhibited peak inflammatory IFN- γ at 48 to 72 hours with negligible IFN-γ production at 6 to 24 hours. By contrast, a high frequency of *memory* CD4 T cells (25-40%) produced IFN-γ within 6 hours of antigen activation with peak production at 24 hours, demonstrating the enhanced kinetics and magnitude of effector cytokine production that is a distinguishing feature of *memory* CD4 T cells. Pet. Ex. 108 at 3-4. Dr. Steinman further illustrated this point by reference to tuberculin testing as described in an article by *Serane et al* which demonstrated that a recall response to a tuberculin test can be read as positive and produce a reaction after 24 hours. Pet. Ex. 105. He also cited to an article by *Kardjito et al.*, which found that the first reaction elicited by a tuberculin test can occur within thirty minutes. Pet. Ex. 107. Dr. Steinman testified that a corollary to the recall response in petitioner is an injection of tuberculin, and that "if you actually had been exposed to tuberculin or had tuberculosis, that arm might be red and angry in 24 hours or less." Tr. 251. While tuberculin testing response is somewhat different than memory response to a vaccine, the study by *Lai* appeared to be particularly on point given the role of CD4 and TH1 effector cells in producing IFNγ and in the rapid recall response by memory T cells to a vaccination in which a previously received antigen is administered.

While Dr. Forsthuber provided a detailed description of immune response kinetics, it appeared that he was essentially describing the response of the naïve immune system to a newly confronted antigen. Dr. Forsthuber argued that the immunological recall response of memory B cells takes about 48-50 hours, followed by the activated B cells undergoing eight or nine cell

[37] Wendy Lai et al., *Transcriptional Control of Rapid Recall by Memory CD4 T Cells*, 187 J. Immunol. 133, 134-35 (2011). [Pet. Ex. 108].

divisions to become plasma blasts and convert into antibody secreting cells. Tr. 515-17. All in all, Dr. Forsthuber testified that it would take at least 4-5 days for B cells to convert into antibody secreting cells capable of causing damage via molecular mimicry. *Id*.

Importantly, it should be noted that the early symptoms, within one to three days appeared to be primarily flu like symptoms which could readily appear within the timeframe described by Dr. Forsthuber. The more clearly neurological symptoms appear to have developed somewhere between the fourth and seventh days post vaccination, and certainly were progressing rapidly by the twelfth day. Given the likelihood of an open blood brain barrier at the time of vaccination this seems like a reasonable timeline even using Dr. Fortsthuber's explanation of immune kinetics.

As Dr. Steinman testified, if it took as long as Dr. Forsthuber described for the vaccine induced memory response to occur we would lose much of the protection provided by vaccines. He said wild bacteria and viruses are not so kind as to give us so long to respond and sometimes the key response is not in neutralizing antibodies but in memory killer T cells which fortunately is very fast. Tr. 252.

Dr. Foley's detailed explanation of the evolution of symptoms particularly those arising from the spinal cord lesion is also particularly helpful in understanding the likely timing of the onset of the immune response. As detailed above, he described the small space in the spinal cord through which travel the corticospinal tracts carrying the motor signals from the brain to the organs and extremities below. He said that when a person develops an enhancing spinal cord lesion as aptly demonstrated on the December 12, MRI, the symptom development usually correlates pretty tightly with the development of the lesions. In this case, he said Mr. Gardner developed a systemic type reaction to the flu shot with flu like symptoms within a couple of days and then experienced increasing neurological symptoms after that. It should be noted that while the mild left leg symptoms of December 1, converted to more significant right leg symptoms by December 7 or 8, Mr. Gardner was still able to walk unassisted on December 10. He was not able to do so by December 12.

Dr. Sriram testified that large enhancing lesions like these tend to take months to develop and mentioned the *Cotton* article to support that opinion. However, *Cotton* demonstrated much the opposite. As noted above, *Cotton* studied relapsing-remitting MS patients with weekly MRIs for eight weeks and bi-weekly scans for an additional sixteen weeks. The authors wrote, "The salient finding of our study is that the majority of new lesions in RRMS demonstrate enhancement for only 1 to 2 weeks."[38] They further stated that the distribution of new enhancing lesions according to the duration of their enhancement is skewed toward enhancement duration of 1 week and less. They did find that more than 55% of new lesions were visible only on one or two weekly scans. They also indicated that ring enhancing lesions, which tend to be volumetrically larger tend to enhance for a longer period of time. They said that the peripheral enhancement represents the active inflammatory area. Mr. Gardner's brain lesion was described as almost completely peripherally enhancing on the December 12, brain scan. Importantly, the *Cotton* authors observed eight peripherally enhancing larger lesions with ring appearance at the

[38] Cotton et al., *supra* note 37, at 643.

time of their detection within one to six days after the beginning of the blood brain barrier breakdown.[39] Consistent with the *Cotton* findings, the petitioner's large lesions did continue to enhance, albeit to a progressively lesser degree at least through the January 26, MRI.

While Dr. Sriram also characterized the lesions as having begun to disappear by January 22, that description did not appear to be exactly accurate. On the second MRI, done on December 22, the enhancing nature of the lesions continued with mild reduction in edema, likely as a treatment effect. By January 26, the enhancement in the brain lesion was substantially diminished but still present and the degree of T2 hyperintensity had also reduced but was still present. In the spinal cord, the T2 hyperintensity was also still 8 cms in length with slight post contrast enhancement. Pet. Ex. 7 at 5.

The respondent filed a paper by *Alghatani et al*, entitled *Tumefactive Demyelinating Lesions: A comprehensive review.*[40] Resp. Ex. A-1. The article defined a tumefactive lesion as one that is an acute, large, (greater than 2 cms) tumor-like demyelinating lesion in the CNS that may occur with surrounding edema, mass effect and ring enhancement. It is a rare variant of MS occurring in an estimated 1-3 per 100,000 cases of MS. *Id.* at 1. The article noted that the clinical presentation of TDL (tumefactive demyelinating lesions) is variable and atypical of demyelinating disease due to the difference in size and location. The mass effect is due to the growing mass on its surroundings and is usually the cause of symptoms due to pushing on or displacing the surrounding tissue. Importantly, the article stated, "Motor, sensory, cognitive, and cerebellar symptoms are predominant, and *they may develop at any time from days to weeks." Id*. at 3.

Given the explanation of the coordinate evolution of imaging findings and symptom development with particular reference to the spinal cord and the dramatic change in both[41] over the course of 12 days, the timing appears to be particularly well explained in this case by the presence of an open blood brain and blood cord barrier at the time of vaccination, as evidence by the left leg tingling on December 1. The open blood brain barrier was likely receptive to the immune stimulation provided by the recall response to the influenza vaccine. Dr. Foley opined Mr. Gardner may have gone on to a garden-variety case of MS with much less devastating symptoms and deficits but for the unfortunate timing of the vaccine administration at a time when he was already experiencing mild symptoms of MS and breakdown of the blood brain barrier. The recall response to the vaccine likely activated CD4 T cells, inflammatory cytokines and effector T cells causing initially flu like symptoms followed in a matter of days to weeks the mostly monophasic and severe attack of tumefactive MS. This more likely than not caused him to experience much more severe symptoms and residuals than he otherwise would have experienced. The *Alghantani* article, filed by respondent, provided ample support for the timing in this case in that it stated that the symptoms generated by the tumefactive lesions may occur in

[39] *Id.* at 645.

[40] Alghatani et al., *Tumefactive Demyelinating Lesions: A comprehensive review*, 14 Multiple Sclerosis and Related Disorders 72 (2017). [Respondent Ex A-1].

[41] While there was no pre-vaccination MRI in the time period immediately before vaccination when Mr. Gardner was minimally symptomatic there had been a brain MRI done in June which showed optic neuritis but no MS lesion burden at all at that time.

days to weeks consistent with Dr. Foley's explanation of the evolution of the symptoms in this case.

For all of the foregoing reasons, I conclude that petitioner has demonstrated by a preponderance of the evidence that the aggravation of Mr. Gardner's multiple sclerosis from a more mild form, to an acute, tumefactive and devastating form was generated by the effect of the recall immune response to the influenza vaccine at a time when the blood brain barrier was likely already opened and such aggravation occurred beginning several days post vaccination. The immune response continued for days to weeks after December 1, well into his hospitalization beginning December 12.

Having concluded that petitioner has proved *Loving* prong six, he has successfully demonstrated all of the *Loving* prongs and is entitled to compensation.

## IV. Conclusion

After a review of the entire record and for the for the foregoing reasons, I have concluded that petitioner has established that the covered flu vaccine more likely than not caused-in-fact the significant aggravation of his multiple sclerosis. He is entitled to compensation. A separate damages order will be issued.

**IT IS SO ORDERED.**

**s/Thomas L. Gowen**
Thomas L. Gowen
Special Master